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(54) Title: COMPOUNDS CONTAINING BASIC AND ACIDIC TERMINI USEFUL AS FIBRINOGEN RECEPTOR ANTAGONISTS		
(57) Abstract This invention relates to novel compounds containing basic and acidic termini, pharmaceutical compositions containing such compounds, processes for preparing such compounds, and to methods of using these compounds, alone or in combination with other therapeutic agents, for the inhibition of platelet aggregation, as thrombolytics, and/or for the treatment of thromboembolic disorders.		

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TITLE

5 Compounds Containing Basic and Acidic Termini
 Useful as Fibrinogen Receptor Antagonists

Cross Reference to Earlier Filed Application

 This application is a continuation-in part of U.S.
10 Patent Application Serial Number 08/174552, filed
 December 28, 1993. The disclosure of this earlier filed
 application is hereby incorporated herein by reference.

FIELD OF THE INVENTION

15 This invention relates to novel compounds
 containing basic and acidic termini, pharmaceutical
 compositions containing such compounds, processes for
 preparing such compounds, and to methods of using these
20 compounds, alone or in combination with other
 therapeutic agents, for the inhibition of platelet
 aggregation, as thrombolytics, and/or for the treatment
 of thromboembolic disorders.

BACKGROUND OF THE INVENTION

25 Hemostasis is the normal physiological process in
 which bleeding from an injured blood vessel is arrested.
 It is a dynamic and complex process in which platelets
30 play a key role. Within seconds of vessel injury,
 resting platelets become activated and are bound to the
 exposed matrix of the injured area by a phenomenon
 called platelet adhesion. Activated platelets also bind
 to each other in a process called platelet aggregation
35 to form a platelet plug. This platelet plug can stop
 bleeding quickly, but it must be reinforced by fibrin

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for long-term effectiveness, until the vessel injury can be permanently repaired.

Thrombosis may be regarded as the pathological condition wherein improper activity of the hemostatic mechanism results in intravascular thrombus formation. Activation of platelets and the resulting platelet aggregation and platelet factor secretion has been associated with different pathophysiological conditions including cardiovascular and cerebrovascular thromboembolic disorders, for example, the thromboembolic disorders associated with unstable angina, myocardial infarction, transient ischemic attack, stroke, atherosclerosis, and diabetes. The contribution of platelets to these disease processes stems from their ability to form aggregates, or platelet thrombi, especially in the arterial wall following injury.

Platelets are known to play an essential role in the maintenance of hemostasis and in the pathogenesis of arterial thrombosis. Platelet activation has been shown to be enhanced during coronary thrombolysis. This can lead to delayed reperfusion and reocclusion. Clinical studies with aspirin, ticlopidine, and a monoclonal antibody for platelet glycoprotein IIb/IIIa provide biochemical evidence for platelet involvement in unstable angina, early stage acute myocardial infarction, transient ischemic attack, cerebral ischemia, and stroke.

Platelets are activated by a wide variety of agonists resulting in platelet shape change, secretion of granular contents and aggregation. Aggregation of platelets serves to further focus clot formation by concentrating activated clotting factors in one site. Several endogenous agonists, including adenosine

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diphosphate (ADP), serotonin, arachidonic acid, thrombin, and collagen, have been identified. Because of the involvement of several endogenous agonists in activating platelet function and aggregation, an inhibitor which acts against all agonists would represent a more efficacious antiplatelet agent than currently available antiplatelet drugs, which are agonist-specific.

10 Current antiplatelet drugs are effective against only one type of agonist; these include aspirin, which acts against arachidonic acid; ticlopidine, which acts against ADP; thromboxane A₂ synthetase inhibitors or receptor antagonists, which act against thromboxane A₂; 15 and hirudin, which acts against thrombin.

 Recently, a common pathway for all known agonists has been identified, namely the platelet glycoprotein IIb/IIIa complex (GPIIb/IIIa or IIb/IIIa), which is the 20 membrane protein mediating platelet aggregation. A recent review of GPIIb/IIIa is provided by Phillips et al. (1991) Cell 65: 359-362. The development of a GPIIb/IIIa antagonist represents a promising new approach for antiplatelet therapy. Recent studies in 25 man with a monoclonal antibody for GPIIb/IIIa indicate the antithrombotic benefit of a GPIIb/IIIa antagonist.

 There is presently a need for a GPIIb/IIIa-specific antiplatelet agent which inhibits the activation and 30 aggregation of platelets in response to any agonist. Such an agent should represent a more efficacious antiplatelet therapy than the currently available agonist-specific platelet inhibitors.

35 GPIIb/IIIa on unstimulated platelets does not bind soluble proteins, but GPIIb/IIIa in activated platelets is known to bind four soluble adhesive proteins, namely

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fibrinogen, von Willebrand factor, fibronectin, and vitronectin. The binding of fibrinogen and von Willebrand factor to GPIIb/IIIa causes platelets to aggregate. The binding of fibrinogen is mediated in part by the Arg-Gly-Asp (RGD) recognition sequence which is common to the adhesive proteins that bind GPIIb/IIIa.

Several RGD-peptidomimetic compounds have been reported which block fibrinogen binding and prevent the formation of platelet thrombi. For example, see: Alig et al. U.S. Patent 5,039,805; Alig et al. European Patent Application Publication Number 381,033 A1; Alig et al. Canadian Patent Application 2,061,661 (European Patent Application Publication Number 505,868); Alig et al. European Patent Application Publication Number 445,796 A2; European Patent Application Publication Number 525,629 (Canadian Patent Application Publication Number 2,074,685); European Patent Application Publication Number 4,512,831; PCT Patent Application 9307867.

Compounds of the present invention represent novel structures which bind to the glycoprotein IIb/IIIa receptor, thereby preventing fibrinogen from binding at its platelet receptor site, leading to efficacy in the prevention of blood platelet aggregation and subsequent clotting disorders.

SUMMARY OF THE INVENTION

This invention provides novel aromatic compounds containing basic and acidic termini of Formula I (described below) which are useful as antagonists of the platelet glycoprotein IIb/IIIa complex. The compounds of the present invention inhibit the binding of fibrinogen to platelet glycoprotein IIb/IIIa complex and inhibit the aggregation of platelets. The present invention also includes pharmaceutical compositions

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containing such compounds of Formula I, and methods of using such compounds for the inhibition of platelet aggregation, as thrombolytics, and/or for the treatment of thromboembolic disorders.

5 The present invention also includes methods of treating thromboembolic disorders by administering a compound of Formula I in combination with one or more second therapeutic agents selected from: anti-coagulants such as warfarin or heparin; anti-platelet agents such
10 as aspirin, piroxicam or ticlopidine; thrombin inhibitors such as boro-peptides, hirudin or argatroban; or thrombolytic agents such as tissue plasminogen activator, anistreplase, urokinase or streptokinase; or combinations thereof.

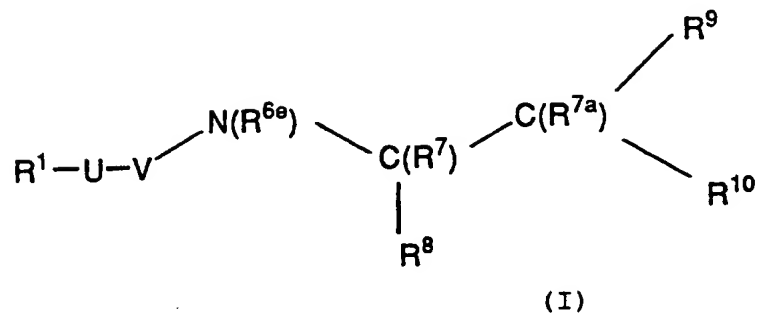
15 Also included in the present invention are pharmaceutical kits comprising one or more containers containing pharmaceutical dosage units comprising a compound of Formula I, for the treatment of thromboembolic disorders.

20 DETAILED DESCRIPTION OF THE INVENTION

 This invention provides novel aromatic compounds containing basic and acidic termini of Formula I (described below) which are useful as antagonists of the
25 platelet glycoprotein IIb/IIIa complex. The compounds of the present invention inhibit the binding of fibrinogen to the platelet glycoprotein IIb/IIIa complex and inhibit the aggregation of platelets. The present invention also includes pharmaceutical compositions
30 containing such compounds of Formula I, and methods of using such compounds for the inhibition of platelet aggregation, as thrombolytics, and/or for the treatment of thromboembolic disorders.

35

This invention provides compounds of Formula I:



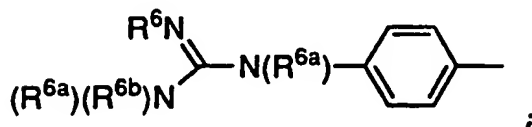
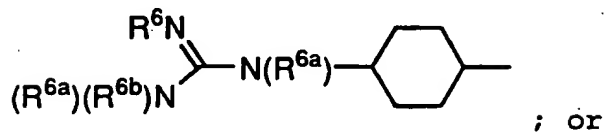
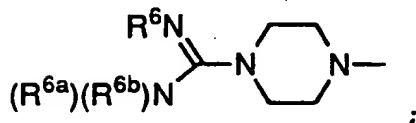
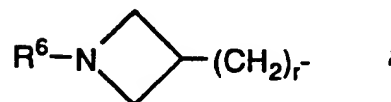
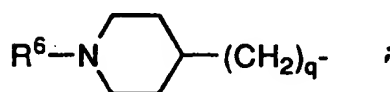
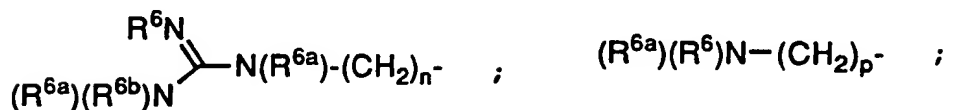
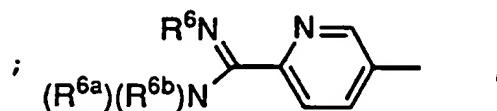
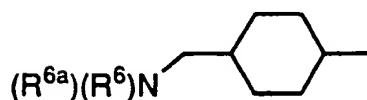
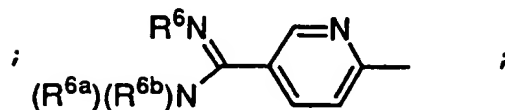
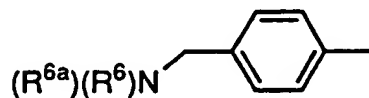
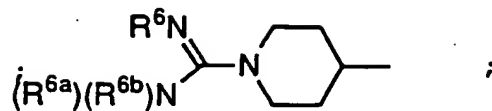
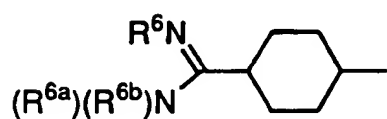
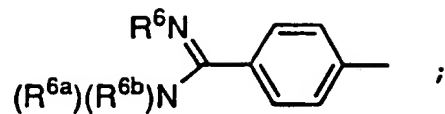
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or pharmaceutically acceptable salt or prodrug forms thereof wherein:

R^1 is selected from:

10

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n is 2, 3, or 4;

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p is 4, 5, or 6;

q is 1, 2, or 3;

5 r is 2, 3, or 4;

R⁶ and R^{6a} are independently selected from: H, C₁-C₁₀ alkyl, C₂-C₆ alkenyl, C₃-C₁₁ cycloalkyl, C₄-C₁₁ cycloalkylalkyl, aryl, aryl(C₁-C₆ alkyl)-, (C₁-C₇ alkyl)carbonyl, arylcarbonyl, (C₁-C₁₀ alkoxy)carbonyl, C₄-C₁₁ cycloalkoxycarbonyl, C₇-C₁₁ bicycloalkoxycarbonyl, aryloxycarbonyl, aryl(C₁-C₁₀ alkyl)carbonyl, or aryl(C₁-C₁₀ alkoxy)carbonyl;

15

R⁷, and R^{7a} are selected independently from: H or C₁-C₄ alkyl;

20

R^{6b} is selected from: H, C₁-C₁₀ alkyl, C₂-C₆ alkenyl, C₃-C₁₁ cycloalkyl, C₄-C₁₅ cycloalkylalkyl, aryl, aryl(C₁-C₁₀ alkyl)-;

25

R^{6e} is selected from: H, C₁-C₁₀ alkyl, C₂-C₆ alkenyl, C₃-C₁₁ cycloalkyl, C₄-C₁₅ cycloalkylalkyl, aryl, aryl(C₁-C₁₀ alkyl)-;

30

Alternatively, R^{6e} and R⁷ can be taken together with the nitrogen and carbon atom to which they are attached to form a 5-7 membered nitrogen heterocycle, said heterocycle optionally including one additional N, O or S atom.

U is selected from:

35

-CH₂-CH₂-CH₂- substituted with 0-4 R³,
-X-CH₂-CH₂- substituted with 0-4 R³,
-CH₂-X-CH₂- substituted with 0-4 R³,
-CH₂-CH₂-X- substituted with 0-4 R³,

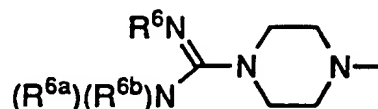
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- CH₂-CH=CH- substituted with 0-4 R³,
 -CH=CH-CH₂- substituted with 0-4 R³,
 -CH₂-C≡C- substituted with 0-2 R³,
 -C≡C-CH₂- substituted with 0-2 R³,
 5 -CH=CH- substituted with 0-2 R³,
 -C≡C-,
 -CH₂-CH₂- substituted with 0-4 R³,
 -X-CH₂- substituted with 0-2 R³,
 -CH₂-X- substituted with 0-2 R³,
 10 -X-, or
 -CH₂- substituted with 0-2 R³;

X is selected from: O, S, S(=O), SO₂, SO₂N(R^{6c}),
 N(R^{6c})SO₂, N(R¹²), C(=O)N(R^{6c}), N(R^{6c})C(=O);

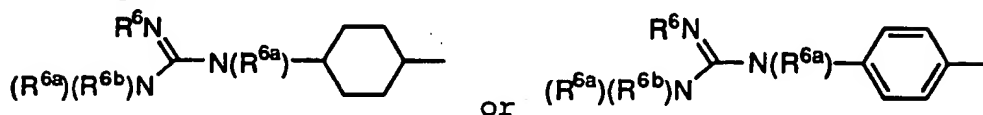
15

with the proviso that when R¹ is



then X is not S, S(=O), or SO₂N(R^{6c});

20 with the proviso that when R¹ is



then U is not optionally substituted -CH₂-CH₂-CH₂-,
 -X-CH₂-CH₂-, -CH₂-X-CH₂-, -CH₂-CH₂-X-, -CH₂-CH=CH-,
 -CH=CH-CH₂-, -CH₂-C≡C-, or -C≡C-CH₂-;

25

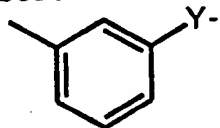
R¹² and R¹³ are independently selected from: H, C₁-C₁₀
 alkyl, C₁-C₁₀ alkoxy carbonyl, C₁-C₁₀ alkyl carbonyl,
 C₁-C₁₀ alkylsulfonyl, aryl(C₁-C₁₀ alkyl)sulfonyl,
 arylsulfonyl, aryl, C₂-C₆ alkenyl, C₃-C₁₁
 cycloalkyl, C₄-C₁₅ cycloalkylalkyl,
 30 aryl(C₁-C₁₀ alkyl), aryl carbonyl, C₄-C₁₁
 cycloalkoxy carbonyl, C₇-C₁₁ bicycloalkoxy carbonyl,
 aryloxy carbonyl, or aryl(C₁-C₁₀ alkoxy) carbonyl;

R^{6c} is selected from: H, C₁-C₁₀ alkyl, C₂-C₆ alkenyl, C₃-C₁₁ cycloalkyl, C₄-C₁₅ cycloalkylalkyl, aryl, aryl(C₁-C₁₀ alkyl)-;

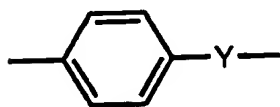
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R³ is independently selected from: H, C₁-C₆ alkyl, C₃-C₆ cycloalkyl, C₄-C₁₁ cycloalkylalkyl, aryl, aryl(C₁-C₆ alkyl)-;

10 V is selected from:



, the phenyl ring being substituted with 0-2 R⁵;



, the phenyl ring being substituted with 0-2 R⁵; or

15

-Q-Y-;

Q is a 5-10 membered heterocyclic ring system having 1-4 heteroatoms selected independently from O, S, and N, said heterocyclic ring being substituted with 0-2 R⁵;

20

Y is selected from: C(=O) or S(O)₂;

25

R⁵ is selected independently from H, F, Cl, Br, I, CF₃, CN, CHO, CO₂R^{5a}, C(=O)R^{5a}, CONHR^{5a}, CON(R^{5a})₂, OC(=O)R^{5a}, OCO₂R^{5a}, OR^{5a}, OC(=O)N(R^{5a})₂, OCH₂CO₂R^{5a}, CO₂CH₂CO₂R^{5a}, N(R¹²)R^{5a}, NO₂, NR^{5a}C(=O)R^{5a}, NR^{5a}C(=O)OR^{5a}, NR^{5a}SO₂N(R¹²)R^{5a}, NR^{5a}SO₂R^{5b}, SR^{5a}, S(=O)R^{5b}, SO₂R^{5b}, SO₂N(R^{5a})₂, C₁ to C₁₀ alkyl, C₂ to C₆ alkenyl, C₂ to C₆ alkynyl, C₃ to C₁₁ cycloalkyl, C₄ to C₁₅ cycloalkylalkyl, aryl, aryl(C₁-C₁₀ alkyl),

30

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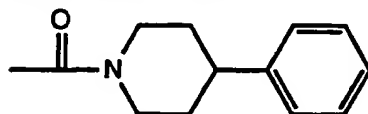
- C₁ to C₆ alkyl substituted with 0-4 R^{5c},
C₂ to C₆ alkenyl substituted with 0-4 R^{5c},
C₂ to C₆ alkynyl substituted with 0-4 R^{5c},
5 C₃ to C₁₁ cycloalkyl substituted with 0-3 R^{5c},
C₄ to C₁₅ cycloalkylalkyl substituted with 0-3 R^{5c},
aryl substituted with 0-3 R^{5c},
aryl(C₁-C₁₀ alkyl) substituted with 0-3 R^{5c};
- 10 R^{5a} is selected from: H, C₁ to C₁₀ alkyl, C₂ to C₆
alkenyl, C₃ to C₁₁ cycloalkyl, C₄ to C₁₅
cycloalkylalkyl, aryl, or aryl(C₁-C₁₀ alkyl);
- R^{5b} is selected from: C₁ to C₁₀ alkyl, C₂ to C₆ alkenyl,
15 C₃ to C₁₅ cycloalkyl, C₄ to C₁₁ cycloalkylalkyl,
aryl, or aryl(C₁-C₁₀ alkyl);
- R^{5c} is selected from: H, halogen, C₁-C₄ alkyl, C₁-C₃
haloalkyl, CN, C₁-C₄ alkoxy, NO₂;
- 20 R⁸ is selected from:
H;
C₁-C₆ alkyl substituted with 0-4 R^{3a};
C₂-C₆ alkenyl substituted with 0-4 R^{3a};
25 C₂-C₆ alkynyl substituted with 0-4 R^{3a};
C₃-C₈ cycloalkyl substituted with 0-4 R^{3a};
aryl substituted with 0-4 R^{3a};
aryl(C₁-C₆ alkyl)- substituted with 0-4 R^{3a};
- 30 a 5-10 membered heterocyclic ring system having 1-4
heteroatoms selected independently from O, S, and
N, said heterocyclic ring being substituted with
0-3 R^{3a};
- 35 C₁-C₆ alkyl substituted with a 5-10 membered
heterocyclic ring system having 1-4 heteroatoms

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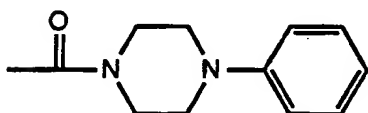
selected independently from O, S, and N, said heterocyclic ring being substituted with 0-4 R^{3a};

(R¹²) (R^{5a})NC(=O)-;

5 piperidyl-C(=O)-;



substituted with 0-4 R^{3a}; or



substituted with 0-4 R^{3a};

10 R^{3a} is selected from H, halogen, C₁-C₈ alkyl, C₂-C₆ alkenyl, C₃-C₁₁ cycloalkyl, C₄-C₁₁ cycloalkylalkyl, aryl, aryl(C₁-C₆ alkyl)-;

R⁹ is selected from:

15 H,
 -R¹⁵,
 -N(R^{6d})C(=O)-O-R^{15a},
 -N(R^{6d})C(=O)-R¹⁵,
 -N(R^{6d})C(=O)-NH-R¹⁵,
 20 -N(R^{6d})NH-C(=O)-O-R^{15a},
 -N(R^{6d})NH-C(=O)-R¹⁵,
 -N(R^{6d})NH-C(=O)-NH-R¹⁵,
 -N(R^{6d})S(=O)₂-O-R^{15b},
 -N(R^{6d})S(=O)₂-R¹⁵,
 25 -N(R^{6d})C(=S)NHR¹⁵,
 -N(R^{6d})P(=S)OR^{15a},
 -N(R^{6d})P(=O)OR^{15a},
 -N(R^{6d})P(=S)(R^{15a})₂,
 -N(R^{6d})P(=O)(R^{15a})₂,
 30 -N(R¹²)(R^{5a}),
 -CH=CH-R¹⁵, or
 -C≡C-R¹⁵;

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with the proviso that when U is -C(=O)NH- or
-C(=O)NHCH₂-, then R⁹ is not H;

5 R^{6d} is selected from: H, C₁-C₁₀ alkyl, C₂-C₆ alkenyl,
C₃-C₁₁ cycloalkyl, C₄-C₁₅ cycloalkylalkyl, aryl,
aryl(C₁-C₁₀ alkyl)-;

R¹⁵ is selected from:

10 H,
C₁-C₈ alkyl substituted with 0-4 R^{3a},
C₂-C₈ alkenyl substituted with 0-4 R^{3a},
C₂-C₈ alkynyl substituted with 0-4 R^{3a},
C₃-C₈ cycloalkyl substituted with 0-4 R^{3a},
aryl substituted with 0-4 R^{3a},
15 aryl(C₁-C₆ alkyl)- substituted with 0-4 R^{3a},

20 a 5-10 membered heterocyclic ring system having 1-4
heteroatoms selected independently from O, S, and
N, said heterocyclic ring being substituted with
0-3 R^{3a},

25 C₁-C₆ alkyl substituted with a 5-10 membered
heterocyclic ring system having 1-4 heteroatoms
selected independently from O, S, and N, said
heterocyclic ring being substituted with 0-4 R^{3a};

R^{15a} is selected from:

30 C₁-C₈ alkyl substituted with 0-4 R^{3a},
C₂-C₈ alkenyl substituted with 0-4 R^{3a},
C₂-C₈ alkynyl substituted with 0-4 R^{3a},
C₃-C₈ cycloalkyl substituted with 0-4 R^{3a},
aryl substituted with 0-4 R^{3a},
aryl(C₁-C₆ alkyl)- substituted with 0-4 R^{3a},

35 a 5-10 membered heterocyclic ring system having 1-4
heteroatoms selected independently from O, S, and

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N, said heterocyclic ring being substituted with
0-3 R^{3a},

5 C₁-C₆ alkyl substituted with a 5-10 membered
heterocyclic ring system having 1-4 heteroatoms
selected independently from O, S, and N, said
heterocyclic ring being substituted with 0-4 R^{3a};

10 R¹⁰ is selected from CO₂R¹⁶, CO₂R^{13b}, SO₃H, tetrazolyl,
or PO₃H;

R¹⁶ is selected from: H, C₁ to C₁₀ alkyl, C₃ to C₁₁
cycloalkyl, aryl, aryl(C₁ to C₆ alkyl)-, C₃ to C₁₀
alkylcarbonyloxyalkyl, C₃ to C₁₀
15 alkoxy carbonyloxyalkyl, C₂ to C₁₀ alkoxy carbonyl,
C₅ to C₁₀ cycloalkylcarbonyloxyalkyl, C₅ to C₁₀
cycloalkoxy carbonyloxyalkyl, C₅ to C₁₀
cycloalkoxy carbonyl, aryloxy carbonyl,
aryloxy carbonyloxy(C₁ to C₆ alkyl)-,
20 arylcarbonyloxy(C₁ to C₆ alkyl)-, C₅ to C₁₂
alkoxyalkylcarbonyloxyalkyl, (5-(C₁-C₅ alkyl)-1,3-
dioxo-cyclopenten-2-one-yl)methyl, (5-aryl-1,3-
dioxo-cyclopenten-2-one-yl)methyl, or
(R¹²) (R^{5a})N-(C₁-C₁₀ alkyl)-.

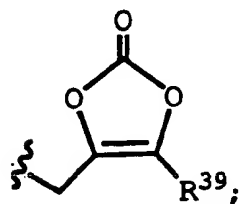
25

R^{13b} is selected independently from:

-CH(R³⁶)OC(=O)R³⁷;

-CH(R³⁶)OC(=O)OR³⁸;

30



R³⁶ is C₁-C₄ linear alkyl or H;

-15-

R³⁷ is selected from:

- (a) H;
- (b) C₁-C₈ alkyl or C₃-C₈ cycloalkyl, said alkyl or cycloalkyl being substituted with 1-2 groups independently selected from:
 - (i) C₁-C₄ alkyl;
 - (ii) C₃-C₈ cycloalkyl;
 - (iii) C₁-C₅ alkoxy;
 - (iv) aryl substituted with 0-2 groups independently selected from: halogen, phenyl, C₁-C₆ alkyl, C₁-C₆ alkoxy, NO₂, -S(C₁-C₅ alkyl), -S(=O)(C₁-C₅ alkyl), -SO₂(C₁-C₅ alkyl), -OH, -N(R¹²)(R^{5a}), -CO₂R^{5a}, -C(=O)N(R¹²)(R^{5a}), or -C_vF_w where v = 1 to 3 and w = 1 to (2v+1);
- (c) aryl substituted with 0-2 groups independently selected from: halogen, phenyl, C₁-C₆ alkyl, C₁-C₆ alkoxy, NO₂, -S(C₁-C₅ alkyl), -S(=O)(C₁-C₅ alkyl), -SO₂(C₁-C₅ alkyl), -OH, -N(R¹²)(R^{5a}), -CO₂R^{5a}, -C(=O)N(R¹²)(R^{5a}), or -C_vF_w where v = 1 to 3 and w = 1 to (2v+1);

R³⁸ is selected from:

- (a) C₁-C₈ alkyl or C₃-C₈ cycloalkyl, said alkyl or cycloalkyl being substituted with 1-2 groups independently selected from:
 - (i) C₁-C₄ alkyl;
 - (ii) C₃-C₈ cycloalkyl;
 - (iii) C₁-C₅ alkoxy;
 - (iv) aryl substituted with 0-2 groups independently selected from: halogen, phenyl, C₁-C₆ alkyl, C₁-C₆ alkoxy, NO₂, -S(C₁-C₅ alkyl), -S(=O)(C₁-C₅ alkyl), -SO₂(C₁-C₅ alkyl), -OH, -N(R¹²)(R^{5a}), -CO₂R^{5a}, -C(=O)N(R¹²)(R^{5a}), or -C_vF_w where v = 1 to 3 and w = 1 to (2v+1);
- (b) aryl substituted with 0-2 groups independently selected from: halogen, phenyl, C₁-C₆ alkyl, C₁-C₆ alkoxy, NO₂, -S(C₁-C₅ alkyl),

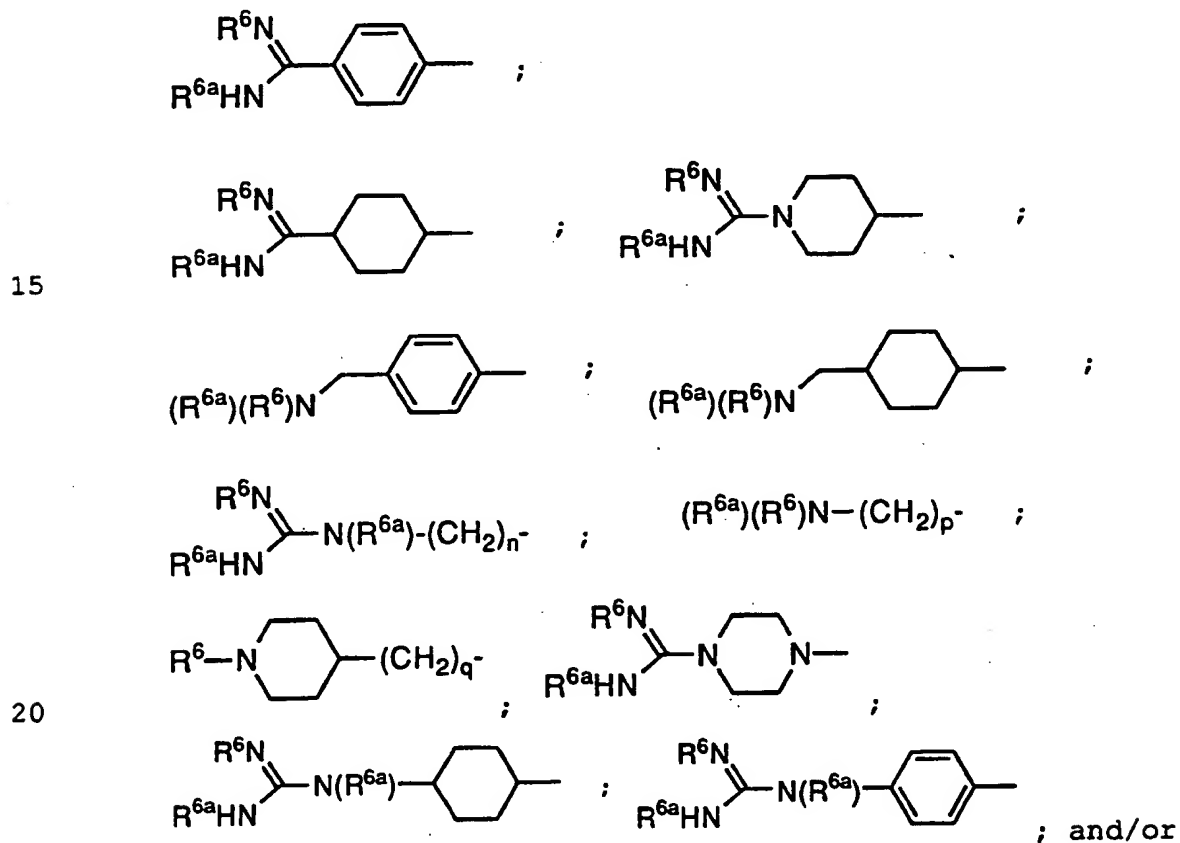
-16-

-S(=O) (C₁-C₅ alkyl), -SO₂ (C₁-C₅ alkyl), -OH,
 -N(R¹²) (R^{5a}), -CO₂R^{5a}, -C(=O)N(R¹²) (R^{5a}), or
 -C_vF_w where v = 1 to 3 and w = 1 to (2v+1);

5 R³⁹ is C₁-C₄ alkyl, benzyl, or phenyl.

Preferred compounds of the present invention are
 those compounds described above of Formula I, or a
 10 pharmaceutically acceptable salt or prodrug form
 thereof, wherein:

R¹ is selected from:



R^{6b}, R^{6e}, R⁷, and R^{7a} are H; and/or

-17-

Alternatively, R^{6e} and R^7 can be taken together with the nitrogen and carbon atom to which they are attached to form a 5-7 membered nitrogen heterocycle, said

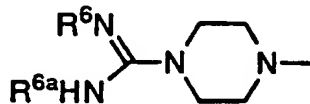
5 heterocycle optionally including one additional N, O or S atom.

U is selected from:

- CH₂-CH₂-CH₂-,
- 10 -X-CH₂-CH₂-,
- CH₂-X-CH₂-,
- CH₂-CH₂-X-,
- CH₂-CH=CH-,
- CH=CH-CH₂-,
- 15 -CH₂-C≡C-,
- C≡C-CH₂-,
- CH=CH-,
- C≡C-,
- CH₂-CH₂-,
- 20 -X-CH₂-,
- CH₂-X-,
- X-,
- CH₂-; and/or

25 X is selected from: O, S, S(=O), SO₂, N(R¹²);

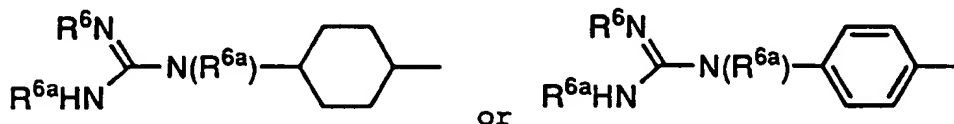
with the proviso that when R^1 is



then X is not S or S(=O);

30

with the proviso that when R^1 is

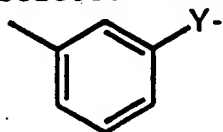


-18-

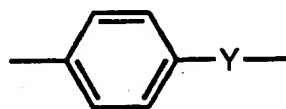
then U is not $-\text{CH}_2-\text{CH}_2-\text{CH}_2-$, $-\text{X}-\text{CH}_2-\text{CH}_2-$,
 $-\text{CH}_2-\text{X}-\text{CH}_2-$, $-\text{CH}_2-\text{CH}_2-\text{X}-$, $-\text{CH}_2-\text{CH}=\text{CH}-$, $-\text{CH}=\text{CH}-\text{CH}_2-$,
 $-\text{CH}_2-\text{C}\equiv\text{C}-$, or $-\text{C}\equiv\text{C}-\text{CH}_2-$; and/or

5 $\text{R}^{6\text{c}}$ is selected from H or C_1-C_4 alkyl; and/or

V is selected from:



substituted with 0-2 R^5 ,



10

substituted with 0-2 R^5 ,

$-\text{Q}-\text{Y}-$; and/or

15 Q is a heterocycle selected from oxazole, isoxazole,
 oxazoline, isoxazoline, thiazole, isothiazole,
 thiazoline, isothiazoline, triazole, imidazole,
 imidazoline, 1,2,4-oxadiazole, 1,2,4-thiadiazole,
 1,3,4-oxadiazole, 1,3,4-thiadiazole, pyridine,
 pyridine N-oxide, thiophene, furan, or pyrrole,
 20 said heterocycle being substituted with 0-2 R^5 ,
 wherein the bonds between Q and Y and between Q and
 U are at the 1 and 3 positions of Q; and/or

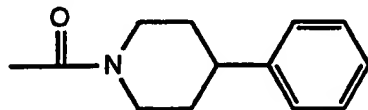
25 R^5 is independently selected from: H, halo, cyano,
 $\text{CO}_2\text{R}^{5\text{a}}$, $\text{OR}^{5\text{a}}$, $\text{OCH}_2\text{CO}_2\text{R}^{5\text{a}}$, NO_2 , $(\text{C}_1-\text{C}_{10}$
 alkyl)carbonyl, $-\text{N}(\text{R}^{12})\text{R}^{5\text{a}}$, C_1-C_{10} alkyl, C_2-C_6
 alkenyl, C_4 to C_{11} cycloalkylmethyl, C_3 to C_{10}
 cycloalkyl, aryl, aryl(C_1-C_6 alkyl)-,

30 aryl substituted with 0-3 $\text{R}^{5\text{c}}$; and/or

$\text{R}^{5\text{a}}$ is selected from: H, C_1 to C_{10} alkyl, C_2 to C_6
 alkenyl, C_4 to C_{11} cycloalkylmethyl,
 aryl(C_1-C_6 alkyl)-; and/or

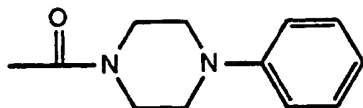
R⁸ is selected from:

- H;
- C₁-C₆ alkyl substituted with 0-4 R^{3a};
- 5 C₂-C₆ alkenyl substituted with 0-4 R^{3a};
- C₂-C₆ alkynyl substituted with 0-4 R^{3a};
- C₃-C₈ cycloalkyl substituted with 0-4 R^{3a};
- aryl substituted with 0-2 R^{3a};
- aryl(C₁-C₆ alkyl)- substituted with 0-2 R^{3a};
- 10 a heterocyclic ring system selected from pyridinyl, furanyl, thiazolyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, benzofuranyl, indolyl, indolenyl, quinolinyl, isoquinolinyl, benzimidazolyl, piperidinyl, tetrahydrofuranyl, pyranal, pyridinyl, 3H-indolyl, indolyl, carbazole, pyrrolidinyl, piperidinyl, indolinyl, or morpholinyl, said heterocyclic ring being substituted with 0-2 R^{3a};
- 15 C₁-C₆ alkyl substituted with a heterocyclic ring system selected from pyridinyl, furanyl, thiazolyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, benzofuranyl, indolyl, indolenyl, quinolinyl, isoquinolinyl, benzimidazolyl, piperidinyl, tetrahydrofuranyl, pyranal, pyridinyl, 3H-indolyl, indolyl, carbazole, pyrrolidinyl, piperidinyl, indolinyl, or morpholinyl, , said heterocyclic ring being substituted with 0-2 R^{3a};
- 20 C₁-C₆ alkyl substituted with a heterocyclic ring system selected from pyridinyl, furanyl, thiazolyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, benzofuranyl, indolyl, indolenyl, quinolinyl, isoquinolinyl, benzimidazolyl, piperidinyl, tetrahydrofuranyl, pyranal, pyridinyl, 3H-indolyl, indolyl, carbazole, pyrrolidinyl, piperidinyl, indolinyl, or morpholinyl, , said heterocyclic ring being substituted with 0-2 R^{3a};
- 25 C₁-C₆ alkyl substituted with a heterocyclic ring system selected from pyridinyl, furanyl, thiazolyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, benzofuranyl, indolyl, indolenyl, quinolinyl, isoquinolinyl, benzimidazolyl, piperidinyl, tetrahydrofuranyl, pyranal, pyridinyl, 3H-indolyl, indolyl, carbazole, pyrrolidinyl, piperidinyl, indolinyl, or morpholinyl, , said heterocyclic ring being substituted with 0-2 R^{3a};
- 30 (R¹²) (R^{5a}) NC(=O)-;
- piperidyl-C(=O)-;



substituted with 0-2 R^{3a}; or

-20-

substituted with 0-2 R^{3a};

and/or

5 R¹² and R¹³ are independently selected from: H, C₁-C₁₀ alkyl, aryl, C₂-C₆ alkenyl, C₄-C₁₁ cycloalkylalkyl, aryl(C₁-C₆ alkyl)-; and/or

10 R^{3a} is selected from H, C₁-C₈ alkyl, C₂-C₆ alkenyl, C₃-C₁₁ cycloalkyl, C₄-C₁₁ cycloalkylalkyl, aryl, aryl(C₁-C₆ alkyl)-; and/or

R⁹ is selected from:

15 H,
-R¹⁵,
-N(R^{6d})C(=O)-O-R^{15a},
-N(R^{6d})C(=O)-R¹⁵,
-N(R^{6d})C(=O)-NH-R¹⁵,
-N(R^{6d})NH-C(=O)-O-R^{15a},
-N(R^{6d})NH-C(=O)-R¹⁵,
20 -N(R^{6d})NH-C(=O)-NH-R¹⁵,
-N(R^{6d})S(=O)₂-R¹⁵,
-N(R¹²)(R^{5a}),
-CH=CH-R¹⁵, or
-C≡C-R¹⁵; and/or

25

R^{6d} is selected from: H or C₁-C₄ alkyl; and/or

R¹⁵ is selected from:

30 H,
C₁-C₈ alkyl substituted with 0-4 R^{3a},
C₂-C₈ alkenyl substituted with 0-4 R^{3a},
C₃-C₈ cycloalkyl substituted with 0-2 R^{3a},
aryl substituted with 0-2 R^{3a},
aryl(C₁-C₆ alkyl)- substituted with 0-2 R^{3a},

35

-21-

- a heterocyclic ring system selected from pyridinyl, furanyl, thiazolyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, benzofuranyl, indolyl, indolenyl, quinolinyl, isoquinolinyl, benzimidazolyl, piperidinyl, tetrahydrofuranyl, pyranyl, pyridinyl, 3H-indolyl, indolyl, carbazole, pyrrolidinyl, piperidinyl, indolinyl, or morpholinyl, said heterocyclic ring being substituted with 0-2 R^{3a},
- 10 C₁-C₆ alkyl substituted with a heterocyclic ring system selected from pyridinyl, furanyl, thiazolyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, benzofuranyl, indolyl, indolenyl, quinolinyl, isoquinolinyl, benzimidazolyl, piperidinyl, tetrahydrofuranyl, pyranyl, pyridinyl, 3H-indolyl, indolyl, carbazole, pyrrolidinyl, piperidinyl, indolinyl, or morpholinyl, said heterocyclic ring being substituted with 0-2 R^{3a}; and/or
- 15 R^{15a} is selected from:
C₁-C₈ alkyl substituted with 0-4 R^{3a},
C₂-C₈ alkenyl substituted with 0-4 R^{3a},
C₃-C₈ cycloalkyl substituted with 0-2 R^{3a},
aryl substituted with 0-2 R^{3a},
25 aryl(C₁-C₆ alkyl)- substituted with 0-2 R^{3a},
- a heterocyclic ring system selected from pyridinyl, furanyl, thiazolyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, benzofuranyl, indolyl, indolenyl, quinolinyl, isoquinolinyl, benzimidazolyl, piperidinyl, tetrahydrofuranyl, pyranyl, pyridinyl, 3H-indolyl, indolyl, carbazole, pyrrolidinyl, piperidinyl, indolinyl, or morpholinyl, said heterocyclic ring being substituted with 0-2 R^{3a},
- 30 C₁-C₆ alkyl substituted with a heterocyclic ring system selected from pyridinyl, furanyl, thiazolyl,
- 35

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thienyl, pyrrolyl, pyrazolyl, imidazolyl,
 benzofuranyl, indolyl, indolenyl, quinolinyl,
 isoquinolinyl, benzimidazolyl, piperidinyl,
 tetrahydrofuranyl, pyranyl, pyridinyl, 3H-indolyl,
 5 indolyl, carbazole, pyrrolidinyl, piperidinyl,
 indolinyl, or morpholinyl, said heterocyclic ring
 being substituted with 0-2 R^{3a}; and/or

R¹⁰ is selected from CO₂R¹⁶; and/or

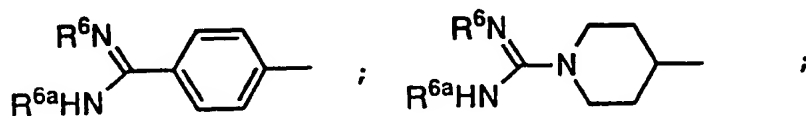
10

R¹⁶ is selected from: H, C₁ to C₁₀ alkyl, C₃ to C₁₁
 cycloalkyl, aryl, aryl(C₁ to C₆ alkyl)-, C₃ to C₁₀
 alkylcarbonyloxyalkyl, C₃ to C₁₀
 alkoxycarbonyloxyalkyl, C₂ to C₁₀ alkoxycarbonyl,
 15 C₅ to C₁₀ cycloalkylcarbonyloxyalkyl, C₅ to C₁₀
 cycloalkoxycarbonyloxyalkyl, C₅ to C₁₀
 cycloalkoxycarbonyl, aryloxy carbonyl,
 aryloxy carbonyloxy(C₁ to C₆ alkyl)-,
 arylcarbonyloxy(C₁ to C₆ alkyl)-, C₅ to C₁₂
 20 alkoxyalkylcarbonyloxyalkyl, (5-(C₁-C₅ alkyl)-1,3-
 dioxo-cyclopenten-2-one-yl)methyl, (5-aryl-1,3-
 dioxo-cyclopenten-2-one-yl)methyl, or
 (R¹²) (R^{5a})N-(C₁-C₁₀ alkyl)-.

25

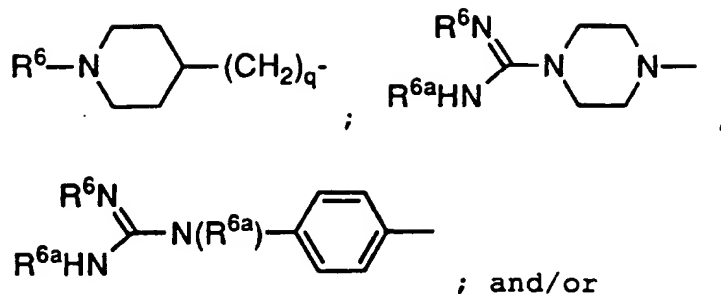
More preferred compounds of the present invention
 are those compounds described above of Formula I, or a
 pharmaceutically acceptable salt or prodrug form
 30 thereof, wherein:

R¹ is selected from:



35

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5 R^{6a}, R^{6b}, R⁷, and R^{7a} are H; and/or

R⁶ is selected from H or C₁-C₄ alkyl; and/or

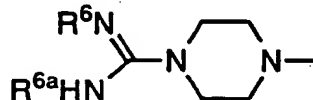
U is selected from:

10 -CH=CH-,
 -C≡C-,
 -CH₂-CH₂-,
 -X-CH₂-,
 -CH₂-X-; and/or

15

X is selected from: O, S, S(=O), SO₂, N(R^{6c});

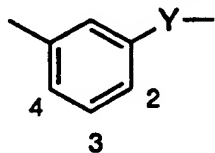
with the proviso that when R^1 is



```
20      then X is not S, S(=0); and/or
```

R^{6c} is selected from H or C₁-C₄ alkyl; and/or

V is selected from:



25 3 substituted at the 2, 3, or 4
 position with 0-1 R⁵,

-Q-Y-; and/or

-24-

Y is -C(=O)-; and/or

Q is a heterocycle selected from oxazole, isoxazole,
oxazoline, isoxazoline, thiazole, isothiazole,
5 thiazoline, isothiazoline, triazole, imidazole,
imidazoline, 1,2,4-oxadiazole, 1,2,4-thiadiazole,
1,3,4-oxadiazole, 1,3,4-thiadiazole, pyridine,
pyridine N-oxide, thiophene, furan, or pyrrole,
said heterocycle being substituted with 0-2 R⁵,
10 wherein the bonds between Q and Y and between Q and
U are at the 1 and 3 positions of Q; and/or

R⁵ is independently selected from: H, halo, cyano,
C₁-C₁₀ alkyl, OR^{5a}, OCH₂CO₂R^{5a}, NO₂, -N(R¹²)R^{5a}, C₄
15 to C₁₁ cycloalkylmethyl, aryl, aryl(C₁-C₆ alkyl)-,

aryl substituted with 0-3 R^{5c}; and/or

R^{5a} is selected from: H, C₁ to C₁₀ alkyl, C₂ to C₆
20 alkenyl, C₄ to C₁₁ cycloalkylmethyl,
aryl(C₁-C₆ alkyl)-; and/or

R^{5c} is selected from: H, halo, cyano, C₁-C₄ alkyl, C₂-C₄
alkenyl, C₁-C₄ alkoxy, NO₂; and/or

25

R⁸ is selected from:

H,

C₁-C₆ alkyl; and/or

30 R⁹ is selected from:

-R¹⁵,

-N(R^{6d})C(=O)-O-R^{15a},

-N(R^{6d})C(=O)-R¹⁵,

-N(R^{6d})S(=O)₂-R¹⁵,

35 -N(R¹²)(R¹³); and/or

R^{6d} is H; and/or

-25-

R¹² and R¹³ are independently selected from: H, C₁-C₁₀ alkyl, C₂-C₆ alkenyl, C₄-C₁₁ cycloalkylalkyl, aryl(C₁-C₆ alkyl)-; and/or

5

R¹⁵ is selected from:

H,

C₁-C₈ alkyl,

C₃-C₈ cycloalkyl,

10

aryl substituted with 0-2 R^{3a},

aryl(C₁-C₆ alkyl)- substituted with 0-2 R^{3a},

a heterocyclic ring system selected from pyridinyl, furanyl, thiazolyl, thienyl, pyrrolyl, pyrazolyl,

15

imidazolyl, benzofuranyl, indolyl, indolenyl,

quinolinyl, isoquinolinyl, benzimidazolyl,

piperidinyl, tetrahydrofuranyl, pyranal, pyridinyl,

3H-indolyl, indolyl, carbazole, pyrrolidinyl,

piperidinyl, indolinyl, or morpholinyl, said

20

heterocyclic ring being substituted with 0-2 R^{3a},

C₁-C₆ alkyl substituted with a heterocyclic ring

system selected from pyridinyl, furanyl, thiazolyl,

thienyl, pyrrolyl, pyrazolyl, imidazolyl,

25

benzofuranyl, indolyl, indolenyl, quinolinyl,

isoquinolinyl, benzimidazolyl, piperidinyl,

tetrahydrofuranyl, pyranal, pyridinyl, 3H-indolyl,

indolyl, carbazole, pyrrolidinyl, piperidinyl,

indolinyl, or morpholinyl, said heterocyclic ring

30

being substituted with 0-2 R^{3a}; and/or

R^{15a} is selected from:

C₁-C₈ alkyl substituted with 0-4 R^{3a},

C₃-C₈ cycloalkyl substituted with 0-2 R^{3a},

35

aryl substituted with 0-2 R^{3a},

aryl(C₁-C₆ alkyl)- substituted with 0-2 R^{3a},

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- a heterocyclic ring system selected from pyridinyl, furanyl, thiazolyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, benzofuranyl, indolyl, indolenyl, quinolinyl, isoquinolinyl, benzimidazolyl, piperidinyl, tetrahydrofuranyl, pyranyl, pyridinyl, 3H-indolyl, indolyl, carbazole, pyrrolidinyl, piperidinyl, indolinyl, or morpholinyl, said heterocyclic ring being substituted with 0-2 R^{3a},
- 10 C₁-C₆ alkyl substituted with a heterocyclic ring system selected from pyridinyl, furanyl, thiazolyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, benzofuranyl, indolyl, indolenyl, quinolinyl, isoquinolinyl, benzimidazolyl, piperidinyl, tetrahydrofuranyl, pyranyl, pyridinyl, 3H-indolyl, indolyl, carbazole, pyrrolidinyl, piperidinyl, indolinyl, or morpholinyl, said heterocyclic ring being substituted with 0-2 R^{3a}; and/or
- 15
- 20 R¹⁰ is selected from CO₂R¹⁶; and/or

R¹⁶ is selected from:

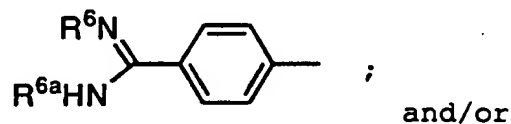
- H;
- C₁ to C₁₀ alkyl;
- 25 methylcarbonyloxymethyl-;
- ethylcarbonyloxymethyl-;
- t-butylcarbonyloxymethyl-;
- cyclohexylcarbonyloxymethyl-;
- 1-(methylcarbonyloxy)ethyl-;
- 30 1-(ethylcarbonyloxy)ethyl-;
- 1-(t-butylcarbonyloxy)ethyl-;
- 1-(cyclohexylcarbonyloxy)ethyl-;
- i-propyloxycarbonyloxymethyl-;
- cyclohexylcarbonyloxymethyl-;
- 35 t-butylloxycarbonyloxymethyl-;
- 1-(i-propyloxycarbonyloxy)ethyl-;
- 1-(cyclohexyloxycarbonyloxy)ethyl-;

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- 1-(*t*-butyloxycarbonyloxy)ethyl-;
 dimethylaminoethyl-;
 diethylaminoethyl-;
 (1,3-dioxo-5-methyl-cyclopenten-2-one-4-yl)methyl-;
 5 (5-(*t*-butyl)-1,3-dioxo-cyclopenten-2-one-4-yl)methyl-;
 (1,3-dioxo-5-phenyl-cyclopenten-2-one-4-yl)methyl-;
 1-(2-(2-methoxypropyl) carbonyloxy) ethyl-.

10

Also preferred compounds of the present invention are those compounds of Formula I described above, or a pharmaceutically acceptable salt or prodrug form thereof, wherein:

R¹ is

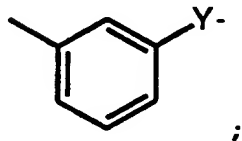
20 R⁶, R^{6a}, R^{6b}, R⁷, and R^{7a} are H; and/or

U is selected from:

-O-CH₂-,
 -CH₂-O-; and/or

25

V is:



Y is -C(=O)-;

30

R⁸ is selected from: H or C₁-C₄ alkyl;

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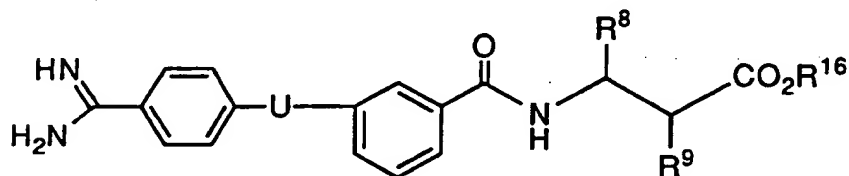
R^9 is selected from: -NHSO₂-phenyl, -NH-Tosyl,
 -NHSO₂(C₁-C₆ alkyl)-, -NH-Cbz, -NHC(=O)(C₁-C₆
 alkoxy), -NHC(=O)(C₁-C₆ alkyl), -NHC(=O)-aryl,
 -NHC(=O)O-(C₁-C₆ alkyl) aryl, -NH(C=O)-(C₁-C₆
 5 alkyl)aryl, -NHC(=O)-3-pyridyl;

R^{10} is selected from CO₂R¹⁶; and/or

R^{16} is selected from: H, C₁ to C₆ alkyl.

10

Specifically preferred compounds of the present
 invention are compounds of Formula I of Formula II:



15

(II)

or a pharmaceutically acceptable salt or prodrug form
 thereof, selected from:

- the compound wherein U is OCH₂, R⁸ is CH₃, R⁹ is H, and
 20 R¹⁶ is H;
 the compound wherein U is OCH₂, R⁸ is H, R⁹ is -NH-Cbz,
 and R¹⁶ is H;
 the compound wherein U is OCH₂, R⁸ is H, R⁹ is -NH-Cbz,
 and R¹⁶ is CH₃;
 25 the compound wherein U is OCH₂, R⁸ is H, R⁹ is -NH-Cbz,
 and R¹⁶ is CH₂CH₃;
 the compound wherein U is CH₂O, R⁸ is CH₃, R⁹ is H, and
 R¹⁶ is H;
 the compound wherein U is CH₂O, R⁸ is CF₃, R⁹ is H, and
 30 R¹⁶ is H;
 the compound wherein U is OCH₂, R⁸ is H, R⁹ is H, and R¹⁶
 is H;
 the compound wherein U is OCH₂, R⁸ is H, R⁹ is -NH-Tosyl,
 and R¹⁶ is H;

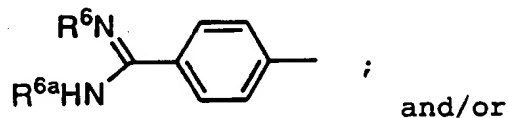
- the compound wherein U is OCH₂, R⁸ is H, R⁹ is -NH-Tosyl, and R¹⁶ is CH₃;
- the compound wherein U is OCH₂, R⁸ is H, R⁹ is -NH-SO₂(CH₂)₃CH₃, and R¹⁶ is H;
- 5 the compound wherein U is OCH₂, R⁸ is H, R⁹ is -NH-SO₂(CH₂)₃CH₃, and R¹⁶ is CH₃;
- the compound wherein U is OCH₂, R⁸ is H, R⁹ is -NH-C(=O)O-C(CH₃)₃, and R¹⁶ is H;
- the compound wherein U is OCH₂, R⁸ is H, R⁹ is -NH-C(=O)O-C(CH₃)₃, and R¹⁶ is CH₃;
- 10 the compound wherein U is OCH₂, R⁸ is H, R⁹ is -NH-C(=O)-(CH₂)₃CH₃, and R¹⁶ is H;
- the compound wherein U is OCH₂, R⁸ is H, R⁹ is -NH-C(=O)-(CH₂)₃CH₃, and R¹⁶ is CH₃;
- 15 the compound wherein U is OCH₂, R⁸ is H, R⁹ is -NH-C(=O)-O(CH₂)₃CH₃, and R¹⁶ is H;
- the compound wherein U is OCH₂, R⁸ is H, R⁹ is -NH-C(=O)-O(CH₂)₃CH₃, and R¹⁶ is CH₃;
- the compound wherein U is OCH₂, R⁸ is H, R⁹ is -NH-C(=O)-(CH₂)₂CH₃, and R¹⁶ is H;
- 20 the compound wherein U is OCH₂, R⁸ is H, R⁹ is -NH-C(=O)-(CH₂)₂CH₃, and R¹⁶ is CH₃;
- the compound wherein U is OCH₂, R⁸ is H, R⁹ is -NH-C(=O)-2-pyridyl, and R¹⁶ is H;
- 25 the compound wherein U is OCH₂, R⁸ is H, R⁹ is -NH-C(=O)-2-pyridyl, and R¹⁶ is CH₃;
- the compound wherein U is OCH₂, R⁸ is H, R⁹ is -NH-C(=O)-3-pyridyl, and R¹⁶ is H;
- the compound wherein U is OCH₂, R⁸ is H, R⁹ is -NH-C(=O)-3-pyridyl, and R¹⁶ is CH₃;
- 30 the compound wherein U is OCH₂, R⁸ is H, R⁹ is -NH-C(=O)-4-pyridyl, and R¹⁶ is H;
- the compound wherein U is OCH₂, R⁸ is H, R⁹ is -NH-C(=O)-4-pyridyl, and R¹⁶ is CH₃;
- 35 the compound wherein U is OCH₂, R⁸ is H, R⁹ is -NH-C(=O)-CH₂-2-pyridyl, and R¹⁶ is H;

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- the compound wherein U is OCH₂, R⁸ is H, R⁹ is -NH-C(=O)-CH₂-2-pyridyl, and R¹⁶ is CH₃;
 the compound wherein U is OCH₂, R⁸ is H, R⁹ is -NH-C(=O)-CH₂-3-pyridyl, and R¹⁶ is H;
 5 the compound wherein U is OCH₂, R⁸ is H, R⁹ is -NH-C(=O)-CH₂-3-pyridyl, and R¹⁶ is CH₃;
 the compound wherein U is OCH₂, R⁸ is H, R⁹ is -NH-C(=O)-CH₂-4-pyridyl, and R¹⁶ is H;
 the compound wherein U is OCH₂, R⁸ is H, R⁹ is -NH-C(=O)-CH₂-4-pyridyl, and R¹⁶ is CH₃;
 10 the compound wherein U is OCH₂, R⁸ is H, R⁹ is -NH-C(=O)-(CH₂)₂-phenyl, and R¹⁶ is H;
 the compound wherein U is OCH₂, R⁸ is H, R⁹ is -NH-C(=O)-(CH₂)₂-phenyl, and R¹⁶ is CH₃;
 15 the compound wherein U is OCH₂, R⁸ is H, R⁹ is -NH₂, and R¹⁶ is H;
 the compound wherein U is OCH₂, R⁸ is H, R⁹ is -NH₂, and R¹⁶ is CH₃.

- 20 Also preferred compounds of the present invention are those compounds of Formula I described above, or a pharmaceutically acceptable salt or prodrug form thereof, wherein:

- 25 R¹ is

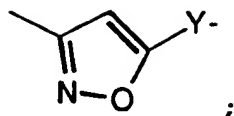


R⁶, R^{6a}, R^{6b}, R⁷, and R^{7a} are H; and/or

- 30 U is selected from:
 -O-CH₂-,
 -CH₂-O-; and/or

V is:

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Y is -C(=O)-;

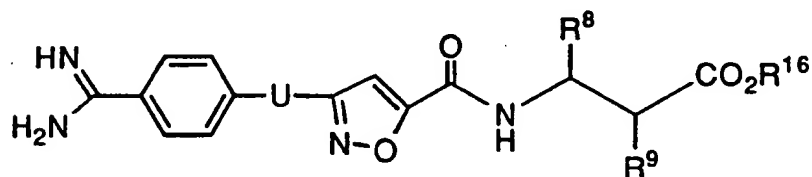
5 R^8 is selected from: H or C_1 - C_4 alkyl;

R^9 is selected from: -NHSO₂-phenyl, -NH-Tosyl,
 -NHSO₂(C_1 - C_6 alkyl)-, -NH-Cbz, -NHC(=O)(C_1 - C_6
 alkoxy), -NHC(=O)(C_1 - C_6 alkyl), -NHC(=O)-aryl,
 10 -NHC(=O)O-(C_1 - C_6 alkyl) aryl, -NH(C=O)-(C_1 - C_6
 alkyl)aryl, -NHC(=O)-3-pyridyl;

R^{10} is selected from CO₂ R^{16} ; and/or

15 R^{16} is selected from: H, C_1 to C_6 alkyl.

Also specifically preferred compounds of the
 present invention are compounds of Formula I of Formula
 20 III:



(III)

or a pharmaceutically acceptable salt or prodrug form
 25 thereof, selected from:
 the compound wherein U is OCH₂, R^8 is CH₃, R^9 is H, and
 R^{16} is H;
 the compound wherein U is OCH₂, R^8 is H, R^9 is -NH-Cbz,
 and R^{16} is H;
 30 the compound wherein U is OCH₂, R^8 is H, R^9 is -NH-Cbz,
 and R^{16} is CH₃;

- the compound wherein U is OCH₂, R⁸ is H, R⁹ is -NH-Cbz,
and R¹⁶ is CH₂CH₃;
- the compound wherein U is CH₂O, R⁸ is CH₃, R⁹ is H, and
R¹⁶ is H;
- 5 the compound wherein U is CH₂O, R⁸ is CF₃, R⁹ is H, and
R¹⁶ is H;
- the compound wherein U is OCH₂, R⁸ is H, R⁹ is H, and R¹⁶
is H;
- the compound wherein U is OCH₂, R⁸ is H, R⁹ is -NH-Tosyl,
10 and R¹⁶ is H;
- the compound wherein U is OCH₂, R⁸ is H, R⁹ is -NH-Tosyl,
and R¹⁶ is CH₃;
- the compound wherein U is OCH₂, R⁸ is H, R⁹ is -NH-
SO₂(CH₂)₃CH₃, and R¹⁶ is H;
- 15 the compound wherein U is OCH₂, R⁸ is H, R⁹ is -NH-
SO₂(CH₂)₃CH₃, and R¹⁶ is CH₃;
- the compound wherein U is OCH₂, R⁸ is H, R⁹ is -NH-
C(=O)O-C(CH₃)₃, and R¹⁶ is H;
- the compound wherein U is OCH₂, R⁸ is H, R⁹ is -NH-
20 C(=O)O-C(CH₃)₃, and R¹⁶ is CH₃;
- the compound wherein U is OCH₂, R⁸ is H, R⁹ is -NH-C(=O)-
(CH₂)₃CH₃, and R¹⁶ is H;
- the compound wherein U is OCH₂, R⁸ is H, R⁹ is -NH-C(=O)-
(CH₂)₃CH₃, and R¹⁶ is CH₃;
- 25 the compound wherein U is OCH₂, R⁸ is H, R⁹ is -NH-C(=O)-
O(CH₂)₃CH₃, and R¹⁶ is H;
- the compound wherein U is OCH₂, R⁸ is H, R⁹ is -NH-C(=O)-
O(CH₂)₃CH₃, and R¹⁶ is CH₃;
- the compound wherein U is OCH₂, R⁸ is H, R⁹ is -NH-C(=O)-
30 (CH₂)₂CH₃, and R¹⁶ is H;
- the compound wherein U is OCH₂, R⁸ is H, R⁹ is -NH-C(=O)-
(CH₂)₂CH₃, and R¹⁶ is CH₃;
- the compound wherein U is OCH₂, R⁸ is H, R⁹ is -NH-C(=O)-
3-pyridyl, and R¹⁶ is H;
- 35 the compound wherein U is OCH₂, R⁸ is H, R⁹ is -NH-C(=O)-
3-pyridyl, and R¹⁶ is CH₃;

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the compound wherein U is OCH₂, R⁸ is H, R⁹ is -NH-C(=O)-(CH₂)₂-phenyl, and R¹⁶ is H;

the compound wherein U is OCH₂, R⁸ is H, R⁹ is -NH-C(=O)-(CH₂)₂-phenyl, and R¹⁶ is CH₃;

5 the compound wherein U is OCH₂, R⁸ is H, R⁹ is -NH₂, and R¹⁶ is H;

the compound wherein U is OCH₂, R⁸ is H, R⁹ is -NH₂, and R¹⁶ is CH₃.

10

In the present invention it has been discovered that the compounds of Formula I above are useful as inhibitors of glycoprotein IIb/IIIa (GPIIb/IIIa). The compounds of the present invention inhibit the
15 activation and aggregation of platelets induced by all known endogenous platelet agonists.

The present invention also provides pharmaceutical compositions comprising a compound of Formula I and a
20 pharmaceutically acceptable carrier.

Also included in the present invention are pharmaceutical kits comprising one or more containers containing pharmaceutical dosage units comprising a compound of Formula I, for the treatment of
25 thromboembolic disorders.

The compounds of Formula I of the present invention are useful for the treatment (including prevention) of thromboembolic disorders. The term thromboembolic disorders as used herein includes conditions involving
30 platelet activation and aggregation, such as arterial or venous cardiovascular or cerebrovascular thromboembolic disorders, including, for example, unstable angina, first or recurrent myocardial infarction, ischemic sudden death, transient ischemic attack, stroke,
35 atherosclerosis, venous thrombosis, deep vein thrombosis, thrombophlebitis, arterial embolism,

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coronary and cerebral arterial thrombosis, myocardial infarction, cerebral embolism, kidney embolisms, pulmonary embolisms, or diabetes, comprising administering to a mammal in need of such treatment a therapeutically effective amount of a compound of Formula I described above.

The compounds of the present invention are useful for inhibiting the binding of fibrinogen to blood platelets, inhibiting aggregation of blood platelets, treating thrombus formation or embolus formation, or preventing thrombus or embolus formation in a mammal. The compounds of the invention may be used as a medicament for blocking fibrinogen from acting at its receptor site in a mammal.

Compounds of the invention may be administered to patients where prevention of thrombosis by inhibiting binding of fibrinogen to the platelet membrane glycoprotein complex IIb/IIIa receptor is desired. They are useful in surgery on peripheral arteries (arterial grafts, carotid endarterectomy) and in cardiovascular surgery where manipulation of arteries and organs, and/or the interaction of platelets with artificial surfaces, leads to platelet aggregation and consumption, and where the aggregated platelets may form thrombi and thromboemboli. The compounds of the present invention may be administered to these surgical patients to prevent the formation of thrombi and thromboemboli.

Extracorporeal circulation is routinely used for cardiovascular surgery in order to oxygenate blood. Platelets adhere to surfaces of the extracorporeal circuit. Adhesion is dependent on the interaction between GPIIb/IIIa on the platelet membranes and fibrinogen adsorbed to the surface of the circuit. Platelets released from artificial surfaces show impaired homeostatic function. Compounds of the invention may be administered to prevent adhesion.

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Other applications of these compounds include prevention of platelet thrombosis, thromboembolism, and reocclusion during and after thrombolytic therapy and prevention of platelet thrombosis, thromboembolism and reocclusion after angioplasty of coronary and other arteries and after coronary artery bypass procedures. The compounds of the present invention may also be used to prevent myocardial infarction. The compounds of the present invention are useful as thrombolytics for the treatment of thromboembolic disorders.

The compounds of the present invention can also be administered in combination with one or more additional therapeutic agents select from: anti-coagulant or coagulation inhibitory agents, such as heparin or warfarin; anti-platelet or platelet inhibitory agents, such as aspirin, piroxicam, or ticlopidine; thrombin inhibitors such as boro-peptides, hirudin or argatroban; or thrombolytic or fibrinolytic agents, such as plasminogen activators, anistreplase, urokinase, or streptokinase.

The compounds of Formula I of the present invention can be administered in combination with one or more of the foregoing additional therapeutic agents, thereby to reduce the doses of each drug required to achieve the desired therapeutic effect. Thus, the combination treatment of the present invention permits the use of lower doses of each component, with reduced adverse, toxic effects of each component. A lower dosage minimizes the potential of side effects of the compounds, thereby providing an increased margin of safety relative to the margin of safety for each component when used as a single agent. Such combination therapies may be employed to achieve synergistic or additive therapeutic effects for the treatment of thromboembolic disorders.

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By "therapeutically effective amount" it is meant an amount of a compound of Formula I that when administered alone or in combination with an additional therapeutic agent to a cell or mammal is effective to prevent or ameliorate the thromboembolic disease condition or the progression of the disease.

By "administered in combination" or "combination therapy" it is meant that the compound of Formula I and one or more additional therapeutic agents are administered concurrently to the mammal being treated. When administered in combination each component may be administered at the same time or sequentially in any order at different points in time. Thus, each component may be administered separately but sufficiently closely in time so as to provide the desired therapeutic effect.

The term anti-coagulant agents (or coagulation inhibitory agents), as used herein, denotes agents that inhibit blood coagulation. Such agents include warfarin (available as CoumadinTM) and heparin.

The term anti-platelet agents (or platelet inhibitory agents), as used herein, denotes agents that inhibit platelet function such as by inhibiting the aggregation, adhesion or granular secretion of platelets. Such agents include the various known non-steroidal anti-inflammatory drugs (NSAIDS) such as aspirin, ibuprofen, naproxen, sulindac, indomethacin, mefenamate, droxicam, diclofenac, sulfinpyrazone, and piroxicam, including pharmaceutically acceptable salts or prodrugs thereof. Of the NSAIDS, aspirin (acetylsalicyclic acid or ASA), and piroxicam. Piroxicam is commercially available from Pfizer Inc. (New York, NY), as FeldaneTM. Other suitable anti-platelet agents include ticlopidine, including pharmaceutically acceptable salts or prodrugs thereof. Ticlopidine is also a preferred compound since it is known to be gentle on the gastro-intestinal tract in

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use. Still other suitable platelet inhibitory agents include thromboxane-A₂-receptor antagonists and thromboxane-A₂-synthetase inhibitors, as well as pharmaceutically acceptable salts or prodrugs thereof.

5 The phrase thrombin inhibitors (or anti-thrombin agents), as used herein, denotes inhibitors of the serine protease thrombin. By inhibiting thrombin, various thrombin-mediated processes, such as thrombin-mediated platelet activation (that is, for
10 example, the aggregation of platelets, and/or the granular secretion of plasminogen activator inhibitor-1 and/or serotonin) and/or fibrin formation are disrupted. Such inhibitors include boro-peptides, hirudin and argatroban, including pharmaceutically acceptable salts
15 and prodrugs thereof. Preferably the thrombin inhibitors are boro-peptides. By boro-peptides, it is meant, N-acetyl and peptide derivatives of boronic acid, such as C-terminal α -aminoboronic acid derivatives of lysine, ornithine, arginine, homoarginine and
20 corresponding isothiuronium analogs thereof. The term hirudin, as used herein, includes suitable derivatives or analogs of hirudin, referred to herein as hirulogs, such as disulfatohirudin. Boro-peptide thrombin inhibitors include compounds described in Kettner et
25 al., U.S. Patent 5,187,157 and European Patent Application Publication Number 293 881 A2, the disclosures of which are hereby incorporated herein by reference. Other suitable boro-peptide thrombin inhibitors include those disclosed in PCT Application
30 Publication Number 92/07869 and European Patent Application Publication Number 471 651 A2, the disclosures of which are hereby incorporated herein by reference, in their entirety.

35 The phrase thrombolytics (or fibrinolytic) agents (or thrombolytics or fibrinolytics), as used herein, denotes agents that lyse blood clots (thrombi). Such agents include tissue plasminogen activator,

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anistreplase, urokinase or streptokinase, including pharmaceutically acceptable salts or prodrugs thereof. Tissue plasminogen activator (tPA) is commercially available from Genentech Inc., South San Francisco, California. The term anistreplase, as used herein, refers to anisoylated plasminogen streptokinase activator complex, as described, for example, in European Patent Application No. 028,489, the disclosures of which are hereby incorporated herein by reference herein, in their entirety. Anistreplase is commercially available as EminaseTM. The term urokinase, as used herein, is intended to denote both dual and single chain urokinase, the latter also being referred to herein as prourokinase.

Administration of the compounds of Formula I of the invention in combination with such additional therapeutic agent, may afford an efficacy advantage over the compounds and agents alone, and may do so while permitting the use of lower doses of each. A lower dosage minimizes the potential of side effects, thereby providing an increased margin of safety.

GPIIb/IIIa is known to be overexpressed in metastatic tumor cells. The compounds or combination products of the present invention may also be useful for the treatment, including prevention, of metastatic cancer.

The compounds herein described may have asymmetric centers. Unless otherwise indicated, all chiral, diastereomeric and racemic forms are included in the present invention. Many geometric isomers of olefins, C=N double bonds, and the like can also be present in the compounds described herein, and all such stable isomers are contemplated in the present invention. It will be appreciated that compounds of the present invention may contain asymmetrically substituted

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carbon atoms, and may be isolated in optically active or racemic forms. It is well known in the art how to prepare optically active forms, such as by resolution of racemic forms or by synthesis, from optically active starting materials. All chiral, diastereomeric, racemic forms and all geometric isomeric forms of a structure are intended, unless the specific stereochemistry or isomer form is specifically indicated.

When any variable (for example but not limited to, R^5 , R^{5a} , and R^6 , p, etc.) occurs more than one time in any constituent or in any formula, its definition on each occurrence is independent of its definition at every other occurrence. Thus, for example, if a group is shown to be substituted with 0-2 R^5 , then said group may optionally be substituted with up to two R^5 and R^5 at each occurrence is selected independently from the defined list of possible R^5 . Also, by way of example, for the group $-N(R^{6a})_2$, each of the two R^{6a} substituents on N is independently selected from the defined list of possible R^{6a} . Similarly, by way of example, for the group $-C(R^7)_2-$, each of the two R^7 substituents on C is independently selected from the defined list of possible R^7 .

When a bond to a substituent is shown to cross the bond connecting two atoms in a ring, then such substituent may be bonded to any atom on the ring.

When a substituent is listed without indicating the atom via which such substituent is bonded to the rest of the compound of Formula I, then such substituent may be bonded via any atom in such substituent. For example, when the substituent is piperazinyl, piperidinyl, or tetrazolyl, unless specified otherwise, said piperazinyl, piperidinyl, tetrazolyl group may be bonded to the rest of the compound of Formula I via any atom in such piperazinyl, piperidinyl, tetrazolyl group.

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Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds. By stable compound or stable structure it is meant herein a compound that is

5 sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

The term "substituted", as used herein, means that any one or more hydrogen on the designated atom is

10 replaced with a selection from the indicated group, provided that the designated atom's normal valency is not exceeded, and that the substitution results in a stable compound. When a substituent is keto (i.e., =O), then 2 hydrogens on the atom are replaced.

15 As used herein, "alkyl" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms; "haloalkyl" is intended to include both branched

20 and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms, substituted with 1 or more halogen (for example $-C_vF_w$ where $v = 1$ to 3 and $w = 1$ to $(2v+1)$); "alkoxy" represents an alkyl group of indicated number of carbon

25 atoms attached through an oxygen bridge; "cycloalkyl" is intended to include saturated ring groups, including mono-, bi- or poly-cyclic ring systems, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, and adamantyl; and

30 "bicycloalkyl" is intended to include saturated bicyclic ring groups such as [3.3.0]bicyclooctane, [4.3.0]bicyclononane, [4.4.0]bicyclodecane (decalin), [2.2.2]bicyclooctane, and so forth. "Alkenyl" is intended to include hydrocarbon chains of either a

35 straight or branched configuration and one or more unsaturated carbon-carbon bonds which may occur in any stable point along the chain, such as ethenyl, propenyl

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and the like; and "alkynyl" is intended to include hydrocarbon chains of either a straight or branched configuration and one or more triple carbon-carbon bonds which may occur in any stable point along the chain, such as ethynyl, propynyl and the like.

The terms "-(alkyl)-", "-(alkylenyl)-", "-(phenyl)-", and the like, refer to alkyl, alkenyl, and phenyl groups, respectively, which are connected by two bonds to the rest of the structure of Formula I. Such groups may alternatively and equivalently be denoted as "alkylene", "alkenylene", "phenylene", and the like, respectively.

"Halo" or "halogen" as used herein refers to fluoro, chloro, bromo and iodo; and "counterion" is used to represent a small, negatively charged species such as chloride, bromide, hydroxide, acetate, sulfate and the like.

As used herein, "aryl" or "aromatic residue" is intended to mean phenyl or naphthyl; the term "arylalkyl" represents an aryl group attached through an alkyl bridge.

As used herein, "carbocycle" or "carbocyclic residue" is intended to mean any stable 3- to 7-membered monocyclic or bicyclic or 7- to 14-membered bicyclic or tricyclic or an up to 26-membered polycyclic carbon ring, any of which may be saturated, partially unsaturated, or aromatic. Examples of such carbocycles include, but are not limited to, cyclopropyl, cyclopentyl, cyclohexyl, phenyl, biphenyl, naphthyl, indanyl, adamantyl, or tetrahydronaphthyl (tetralin).

As used herein, the term "heterocycle" or "heteroaryl" or "heterocyclic" is intended to mean a stable 5- to 7-membered monocyclic or bicyclic or 7- to 10-membered bicyclic heterocyclic ring which may be saturated, partially unsaturated, or aromatic, and which

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consists of carbon atoms and from 1 to 4 heteroatoms independently selected from the group consisting of N, O and S and wherein the nitrogen and sulfur heteroatoms may optionally be oxidized, and the nitrogen may optionally be quaternized, and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The heterocyclic ring may be attached to its pendant group at any heteroatom or carbon atom which results in a stable structure. The heterocyclic rings described herein may be substituted on carbon or on a nitrogen atom if the resulting compound is stable. Examples of such heterocycles include, but are not limited to, pyridyl (pyridinyl), pyrimidinyl, furanyl (furyl), thiazolyl, isothiazolyl, thiazolinyl, isothiazolinyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, tetrazolyl, benzofuranyl, benzothiophenyl, indolyl, indolenyl, quinolinyl, isoquinolinyl, benzimidazolyl, piperidinyl, 4-piperidonyl, pyrrolidinyl, 2-pyrrolidonyl, pyrrolinyl, tetrahydrofuranyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, decahydroquinolinyl or octahydroisoquinolinyl, azocinyl, triazinyl, 6H-1,2,5-thiadiazinyl, 2H,6H-1,5,2-dithiazinyl, thianthrenyl, pyranyl, isobenzofuranyl, chromenyl, xanthenyl, phenoxathiinyl, 2H-pyrrolyl, pyrrolyl, imidazolyl, pyrazolyl, isothiazolyl, isoxazolyl, oxazoline, isoxazoline, oxazolyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, indolizinyl, isoindolyl, 3H-indolyl, indolyl, 1H-indazolyl, purinyl, 4H-quinolizinyl, isoquinolinyl, quinolinyl, phthalazinyl, naphthyridinyl, quinoxalinyl, quinazolinyl, cinnolinyl, pteridinyl, 4aH-carbazole, carbazole, β -carbolinyl, phenanthridinyl, acridinyl, perimidinyl, phenanthrolinyl, phenazinyl, phenarsazinyl, phenothiazinyl, furazanyl, phenoxazinyl, isochromanyl, chromanyl, pyrrolidinyl, pyrrolinyl, imidazolidinyl, imidazolinyl, pyrazolidinyl, pyrazolinyl, piperidinyl,

piperazinyl, indolinyl, isoindolinyl, quinuclidinyl, morpholinyl or oxazolidinyl. Also included are fused ring and spiro compounds containing, for example, the above heterocycles.

5

As used herein, "pharmaceutically acceptable salts" refer to derivatives of the disclosed compounds wherein the parent compound of Formula I is modified by making acid or base salts of the compound of Formula I.

10 Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like.

15

"Prodrugs" are considered to be any covalently bonded carriers which release the active parent drug according to Formula I *in vivo* when such prodrug is administered to a mammalian subject. Prodrugs of the
20 compounds of Formula I are prepared by modifying functional groups present in the compounds in such a way that the modifications are cleaved, either in routine manipulation or *in vivo*, to the parent compounds. Prodrugs include compounds of Formula I wherein
25 hydroxyl, amino, sulfhydryl, or carboxyl groups are bonded to any group that, when administered to a mammalian subject, cleaves to form a free hydroxyl, amino, sulfhydryl, or carboxyl group respectively. Examples of prodrugs include, but are not limited to,
30 acetate, formate and benzoate derivatives of alcohol and amine functional groups in the compounds of Formula I, and the like. Examples of representative carboxyl and amino prodrugs are included under the definition of R⁶, R^{6a}, and R¹⁶.

35

As used herein, the term "amine protecting group" means any group known in the art of organic synthesis

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for the protection of amine groups. Such amine protecting groups include those listed in Greene, "Protective Groups in Organic Synthesis" John Wiley & Sons, New York (1981) and "The Peptides: Analysis, Synthesis, Biology, Vol. 3, Academic Press, New York (1981), the disclosure of which is hereby incorporated by reference. Any amine protecting group known in the art can be used. Examples of amine protecting groups include, but are not limited to, the following: 1) acyl types such as formyl, trifluoroacetyl, phthalyl, and p-toluenesulfonyl (Tosyl); 2) aromatic carbamate types such as benzyloxycarbonyl (Cbz; carbobenzyloxy) and substituted benzyloxycarbonyls, 1-(p-biphenyl)-1-methylethoxycarbonyl, and 9-fluorenylmethyloxycarbonyl (Fmoc); 3) aliphatic carbamate types such as tert-butyloxycarbonyl (Boc), ethoxycarbonyl, diisopropylmethoxycarbonyl, and allyloxycarbonyl; 4) cyclic alkyl carbamate types such as cyclopentyloxycarbonyl and adamantyloxycarbonyl; 5) alkyl types such as triphenylmethyl and benzyl; 6) trialkylsilane such as trimethylsilane; and 7) thiol containing types such as phenylthiocarbonyl and dithiasuccinoyl. Also included in the term "amine protecting group" are acyl groups such as azidobenzoyl, p-benzoylbenzoyl, o-benzylbenzoyl, p-acetylbenzoyl, dansyl, glycyl-p-benzoylbenzoyl, phenylbenzoyl, m-benzoylbenzoyl, benzoylbenzoyl.

The pharmaceutically acceptable salts of the compounds of Formula I include the conventional non-toxic salts or the quaternary ammonium salts of the compounds of Formula I formed, for example, from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like; and the salts prepared from organic acids such as acetic,

-45-

propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, 5 toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, and the like.

The pharmaceutically acceptable salts of the present invention can be synthesized from the compounds of Formula I which contain a basic or acidic moiety by 10 conventional chemical methods. Generally, the salts are prepared by reacting the free base or acid with stoichiometric amounts or with an excess of the desired salt-forming inorganic or organic acid or base in a suitable solvent or various combinations of solvents.

15 The pharmaceutically acceptable salts of the acids of Formula I with an appropriate amount of a base, such as an alkali or alkaline earth metal hydroxide e.g. sodium, potassium, lithium, calcium, or magnesium, or an organic base such as an amine, e.g., 20 dibenzylethylenediamine, trimethylamine, piperidine, pyrrolidine, benzylamine and the like, or a quaternary ammonium hydroxide such as tetramethylammonium hydroxide and the like.

As discussed above, pharmaceutically acceptable 25 salts of the compounds of the invention can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid, respectively, in water or in an organic solvent, or in a mixture of the two; 30 generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists of suitable salts are found in Remington's Pharmaceutical Sciences, 17th ed., Mack Publishing Company, Easton, PA, 1985, p. 1418, the disclosure of 35 which is hereby incorporated by reference.

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The disclosures of all of the references cited herein are hereby incorporated herein by reference in their entirety.

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ammonium hydroxide such as tetramethylammonium hydroxide and the like.

As discussed above, pharmaceutically acceptable salts of the compounds of the invention can be prepared
5 by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid, respectively, in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media like ether, ethyl acetate,
10 ethanol, isopropanol, or acetonitrile are preferred. Lists of suitable salts are found in Remington's Pharmaceutical Sciences, 17th ed., Mack Publishing Company, Easton, PA, 1985, p. 1418, the disclosure of which is hereby incorporated by reference.

15

The disclosures of all of the references cited herein are hereby incorporated herein by reference in their entirety.

Synthesis

The compounds of the present invention can be prepared in a number of ways well known to one skilled in the art of organic synthesis. The compounds of the present invention can be synthesized using the methods described below, together with synthetic methods known in the art of synthetic organic chemistry, or variations thereon as appreciated by those skilled in the art.

Preferred methods include, but are not limited to, those described below. All references cited herein are hereby incorporated in their entirety herein by reference. All the temperatures are reported herein in degrees Celsius.

The following abbreviations are used herein:

β -Ala	3-aminopropionic acid
Boc	tert-butyloxycarbonyl
Boc ₂ O	di-tert-butyl dicarbonate
20 BSTFA	N,O-bis(trimethylsilyl)trifluoromethyl-acetamide
Cbz	benzyloxycarbonyl
DCC	1,3-dicyclohexylcarbodiimide
DEAD	diethyl azodicarboxylate
25 DEC	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
DIEA	diisopropylethylamine
DCHA	dicyclohexylamine
DCM	dichloromethane
30 DMAP	4-dimethylaminopyridine
DMF	N,N-dimethylformamide
EtOAc	ethyl acetate
EtOH	ethyl alcohol
HOBt	1-hydroxybenzotriazole
35 IBCF	iso-butyl chloroformate
LAH	lithium aluminum hydride
NCS	N-chlorosuccinimide

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NMM	<i>N</i> -methyilmorpholine
PPh ₃	triphenylphosphine
pyr	pyridine
TBTU	2-(1H-Benzotriazol-1-yl)-1,1,3,3-
5	tetramethyluronium tetrafluoroborate
TFA	trifluoroacetic acid
THF	tetrahydrofuran

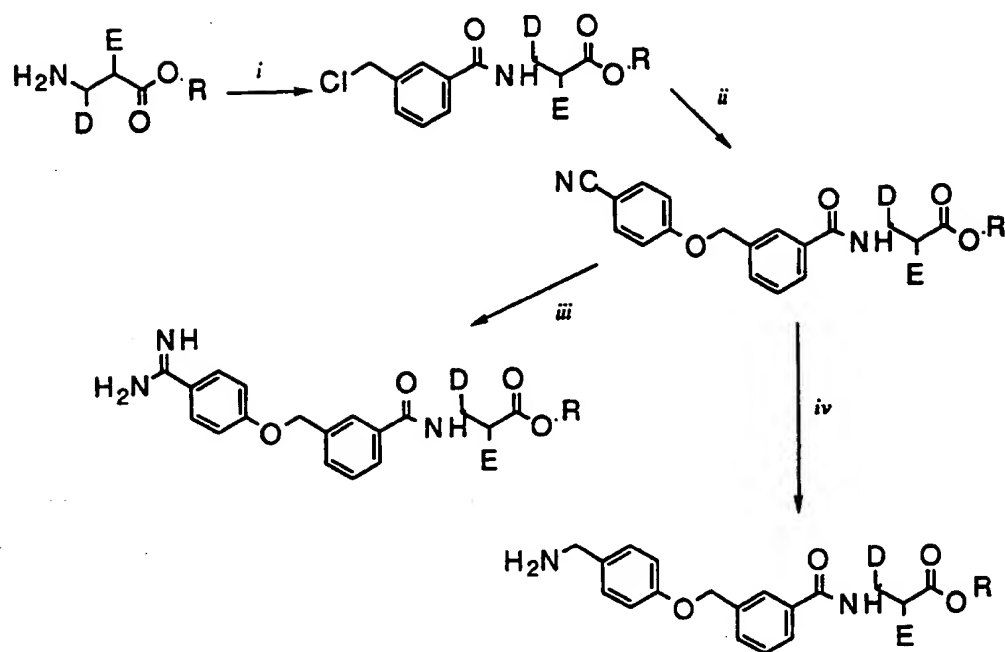
10 The compounds included in this invention can be prepared by methods familiar to one skilled in the art of organic synthesis. For instance, the syntheses of the more preferred classes of compounds are described in the following Schemes.

15 When the compound of interest contains an aryl amidine connected to the central phenyl ring (group V in Formula I) by an O-CH₂ linking group the structure can be prepared as described in Scheme I. Similar methods can be used to prepare the corresponding aminomethyl
20 compounds (Scheme I). The aminomethyl group can be N-alkylated by treatment of the primary amine with a ketone plus NaBH₃CN (*Synthesis* 135 (1975); *Organic Preparations and Procedures*, International 17, 317 (1983)).

25

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Scheme I

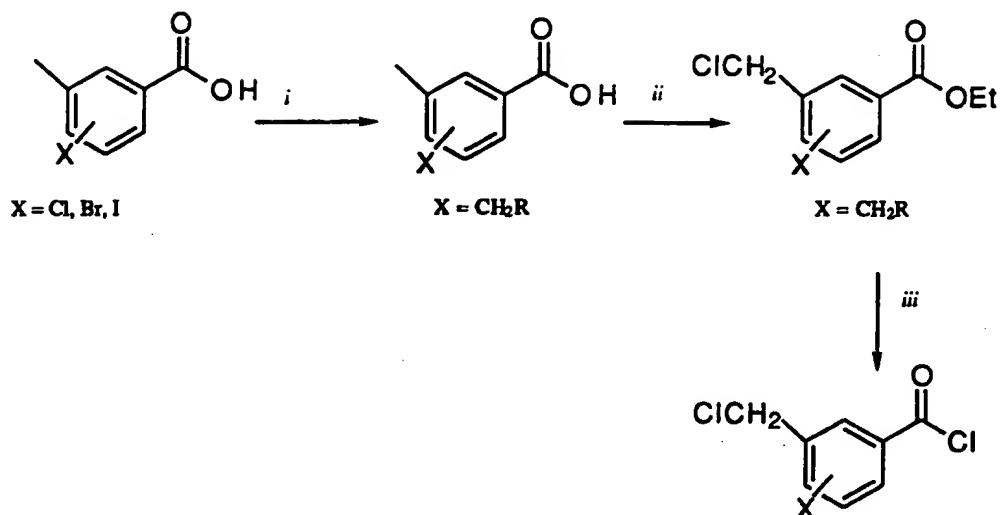


Reagents: i) 3-(chloromethyl)benzoyl chloride, triethylamine, methylene chloride; ii) 4-cyanophenol, K_2CO_3 or NaH ; iii) 1) HCl /methanol, 2) ammonia in methanol, or 1) H_2S /triethylamine, 2) MeI , 3) NH_3 ; iv) HCl , H_2 , Pd/C or H_2/PtO_2

- 5 In Scheme I, the groups R, E, and D correspond to R^{16} , R^9 , and R^8 , respectively, in the compounds of Formula I described above.

- 10 Alkyl substituents on the central phenyl ring (V in Formula I) can be introduced at the beginning of the synthetic procedure as described in Scheme II.

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Scheme II

5 Reagents:

i) 1) n-butyl lithium, 2) RCH(=O) , 3) HCl , H_2 Pd/C or Raney Nickle;

ii) 1) HCl/EtOH , 2) SO_2Cl_2 ;

iii) 1) LiOTMS , 2) SOCl_2 or PCl_5 .

10 Substituent X in Scheme II corresponds to R^5 in the compounds of Formula I described above.

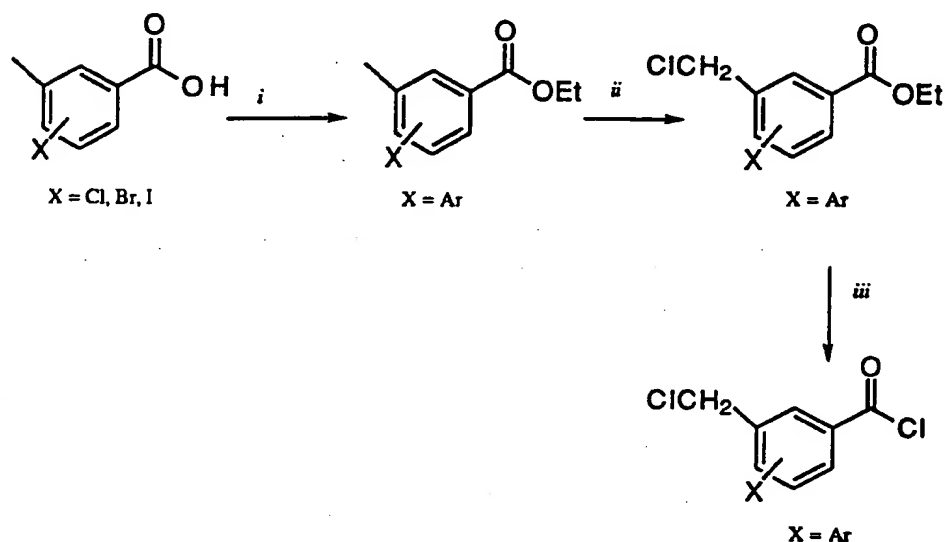
Similarly, hydroxy or alkoxy substituents can be introduced by reacting the lithiated species generated in the first reaction of Scheme II with bis(trimethylsilyl) peroxide to give the silyl ether (Taddei and Ricci, *Synthesis* 633-635 (1986)). The silyl ether can be converted to the phenolic compound by treatment with TBAF or with HCl . The carboxylate is then protected via the ethyl ester (HCl/ethanol), and the phenol converted to an alkyl aryl ether by treatment with an alkyl halide and a base such as K_2CO_3 . Benzylic chlorination, saponification, and conversion to the acid chloride are then accomplished as in the final steps of Scheme II.

Aryl substituted derivatives of 3-(chloromethyl)benzoyl chloride can be prepared by

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Scheme III in which the aryl-aryl bond is formed using the Suzuki coupling procedure (Miyaura, Yanagi, Suzuki, *Synth. Commun.* **11**, 513 (1981); Sharp, Snieckus, *Tetrahedron Lett.* **26**, 5997 (1985)).

5

Scheme III

Reagents:

- 10 i) 1) HCl/EtOH, 2) Ar-B(OH)₂, Pd(PPh₃)₄;
 ii) SO₂Cl₂;
 iii 1) LiOTMS, 2) SOCl₂ or PCl₅.

15 Substituent X in Scheme III corresponds to R⁵ in the compounds of Formula I described above.

Methods for the synthesis of beta amino acids (H₂N-CHR⁸-CH₂-COOH) (used in Scheme I) have been described previously in European Patent Application Publication Number 542,708, and PCT Patent Applications
 20 WO 93/07867, WO 93/12074, and WO 93/16038, the disclosures of which are hereby incorporated by reference.

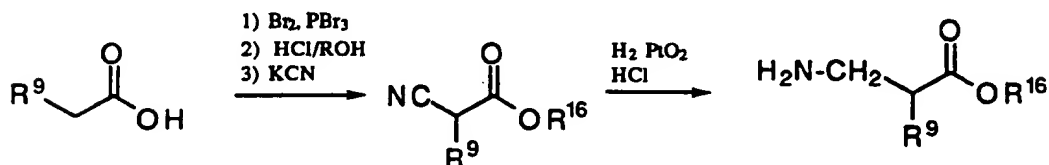
General methods for protection of the carboxylate group have been discussed in T. H. Greene, *Protective Groups in Organic Synthesis* (Wiley-Interscience, 1980),
 25 the disclosure of which is hereby incorporated by

reference. Carboxylate protecting groups useful for peptide synthesis have been reviewed (R. W. Roeske, in *The Peptides*, Vol 3; Protection of functional groups in peptide synthesis, 1981, pp 1-99; Academic Press).

5 The synthesis of N²-substituted 2,3-diamino propionic derivatives can be carried out via Hoffman rearrangement of a wide variety of asparagine derivatives as described in *Synthesis*, 266-267 (1981), the disclosure of which is hereby incorporated by reference.

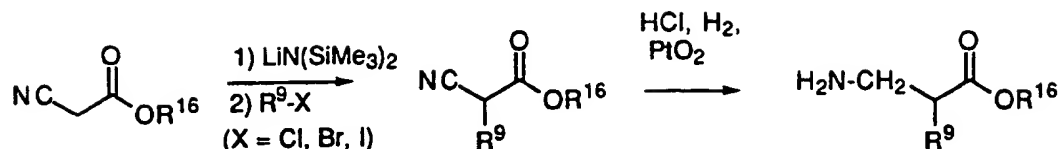
10 Homo beta amino acids (H₂N-CH₂-CHR⁹-COOH) can be synthesized from a variety of carboxylic acids as described in Scheme IV. α-Halogenation of a carboxylic acid (Harwood, *Chem. Rev.* **62**, 99-154 (1962)) followed by displacement of the halogen with KCN gives a nitrile,
15 which upon reduction (as described in *Tett. Lett.*, 4393 (1975); *Modern Synthetic Reactions*, H.O. House (1972); or Harting et al., *J. Am. Chem. Soc.*, 50: 3370 (1928)) provides the desired 3-amino-propionic acid derivative.

20

Scheme IV

25 Alternatively, homo beta amino acids in which R⁹ is an alkyl group can be prepared from esters of 2-(cyano)acetic acid as described in Scheme V by alkylation (Kauer, Erickson-Viitanen, Wolfe, DeGrado, *J. Biol. Chem.* **261**, 10695-10700 (1986)) followed by reduction of the nitrile.

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Scheme V

5 In Scheme I the 3-(chloromethyl)benzoic acid group is coupled to the 3-amino-propionic acid derivative using the acid chloride methods. Other methods for the coupling of carboxylates to amino acid derivatives have been reviewed previously (E. Gross and J. Meienhofer,

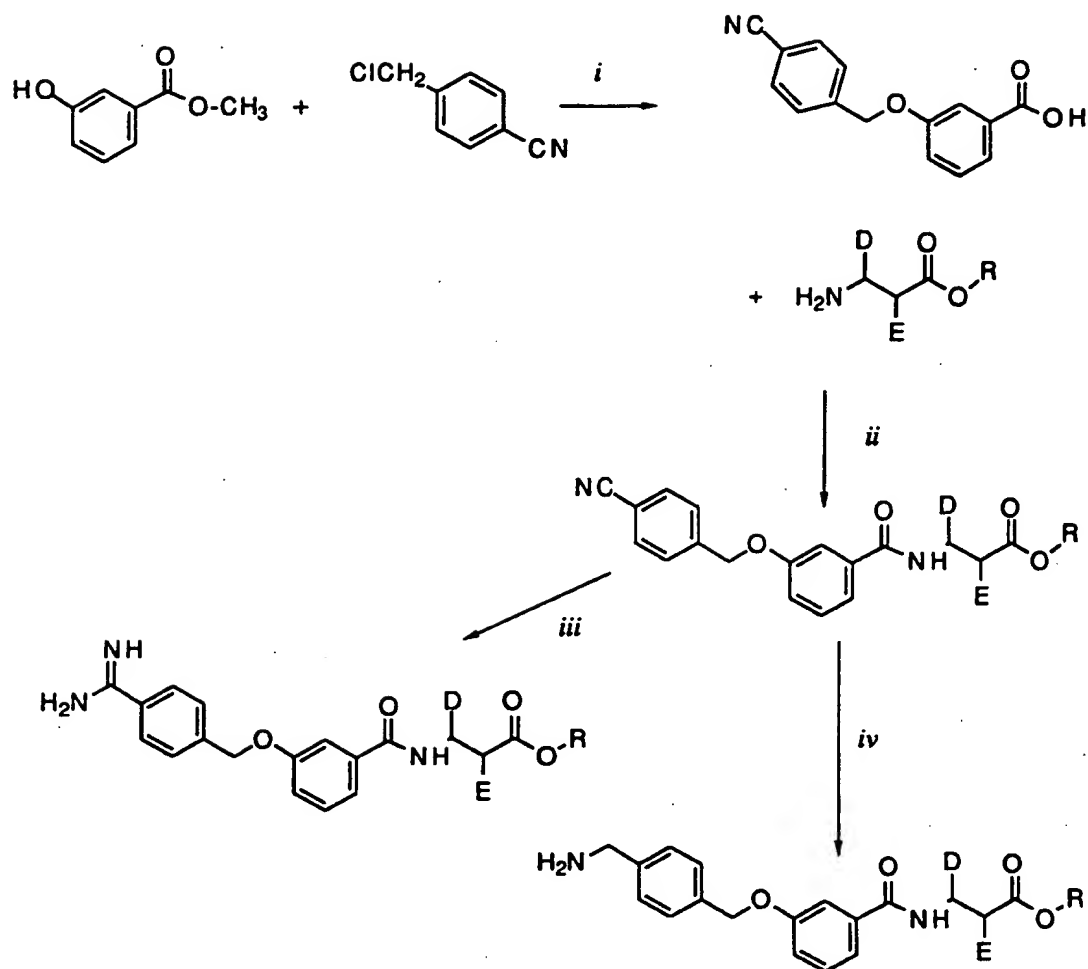
10 eds, The Peptides, Vol. 1, Major methods of peptide bond formation, 1979, Academic Press).

 When the compound of interest contains an aryl amidine connected to the central phenyl ring (V in Formula I) by an CH₂-O linking group the structure can

15 be prepared as described in Scheme VI. Similar methods can be used to prepare the corresponding aminomethyl compounds (Scheme VI). The aminomethyl group can be N-alkylated by treatment of the primary amine with a ketone plus NaBH₃CN (*Synthesis* 135 (1975); *Organic*

20 Preparations and Procedures, International 17: 317 (1983)).

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Scheme VI

Reagents: *i*) 1) K_2CO_3 or NaH 2) LiOH or LiOTMS ; *ii*) DCC or $\text{TBTU}/\text{Et}_3\text{N}$; *iii*) 1) $\text{HCl}/\text{methanol}$, 2) ammonia in methanol; or 1) $\text{H}_2\text{S}/\text{triethylamine}$, 2) MeI , 3) NH_3 ; *iv*) HCl , H_2 Pd/C or HCl , H_2/PtO_2

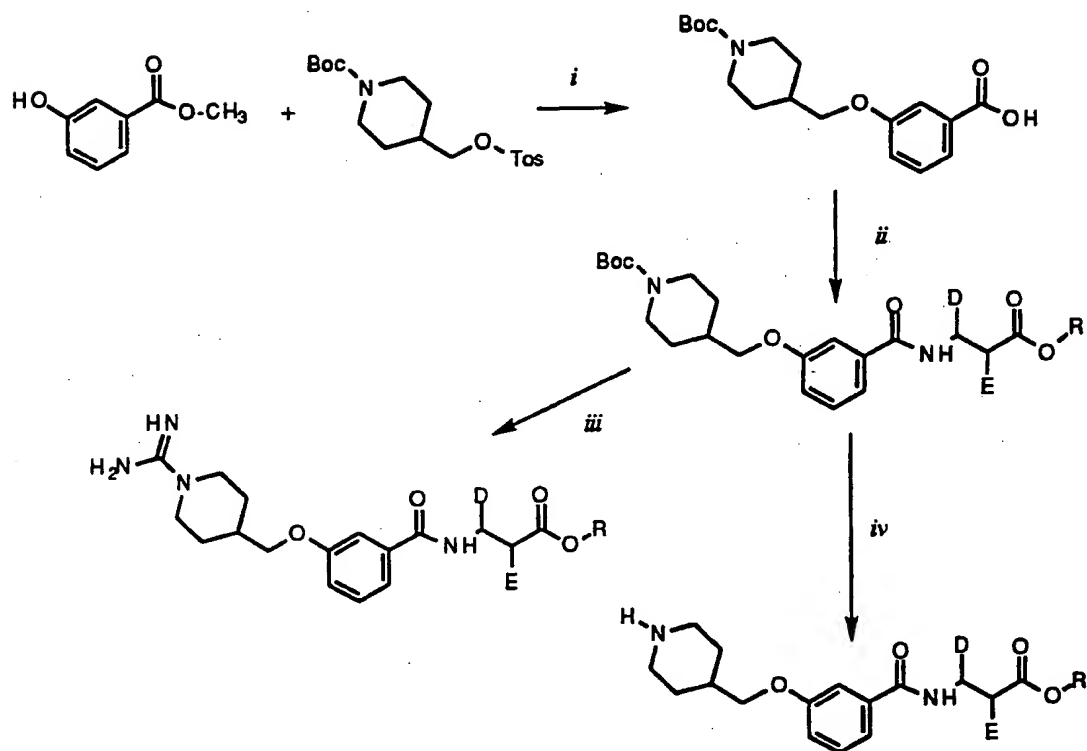
5 In Scheme VI, the substituents E, R, and D correspond to R^9 , R^{16} , and R^8 , respectively, in the compounds of Formula I described above.

10 When the compound of interest contains a piperidine or an N-amidino piperidine connected to the central phenyl ring (V in Formula I) by a $(\text{CH}_2)_n\text{-O}$ linking group the structure can be prepared as described in Scheme

VII, in which $n = 1$. Examples in which n is zero or greater than one can be prepared by analogous methods.

Scheme VII

5



Reagents: i) 1) K_2CO_3 or NaH ; 2) $LiOH$ or $LiOTMS$ ii) DCC or $TBTU/Et_3N$; iii) 1) TFA , 2) $H_2N-C(=NH)-SEt/Et_3N$ or $H_2N-C(=NH)-SO_3H/DMAP$; iv) TFA

In Scheme VII, the substituents E, R, and D correspond to R^9 , R^{16} , and R^8 , respectively, in the compounds of Formula I described above.

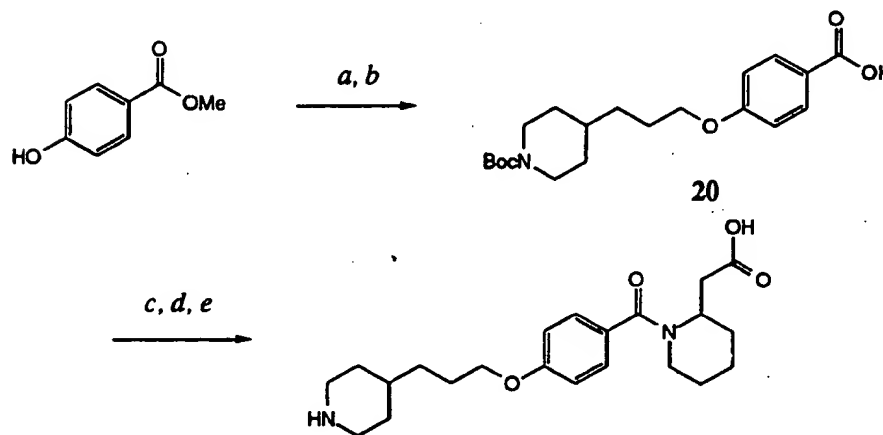
Using the analogous route depicted in Scheme VIIa, compounds with a piperidine or an N-amidino piperidine connected to the central phenyl ring (V in Formula I) by a $(CH_2)_n-O$ linking group where R^{6c} and R^7 are taken together with the nitrogen and carbon atoms to which they are attached to form a N-heterocycle can be prepared. Methyl *p*-hydroxybenzoate is alkylated with a Boc-protected piperidylalkyl alcohol. Saponification and TBTU-mediated coupling to 2-piperidinyllacetic acid

-57-

followed by deprotection gives the desired amino acid. Further elaboration of the piperidine to the amidinopiperidine can be carried out, as described above, prior to final hydrolysis of the ester. The substitution of other cyclic aminoester for 2-piperidinylacetic acid provides additional examples of this group of compounds.

Scheme VIIa

10

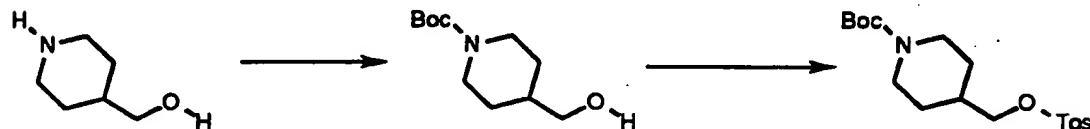


Reagents: *a*. Boc-amino alcohol, PPh_3 , DEAD, THF; *b*. LiOH , THF/ H_2O *c*. β -amino ester, Et_3N , TBTU, DMF; *d*. LiOH , THF/ H_2O ; *e*. 33% TFA/ CH_2Cl_2

Piperidines used in Scheme VII can be prepared from hydroxypiperidines as described in Scheme VIII.

15

Scheme VIII



Reaction conditions: *i*) Boc-ON/triethylamine or di-*t*-butyl-dicarbonate/triethylamine; *ii*) *p*-toluenesulfonic anhydride/triethylamine or *p*-toluenesulfonyl chloride/triethylamine.

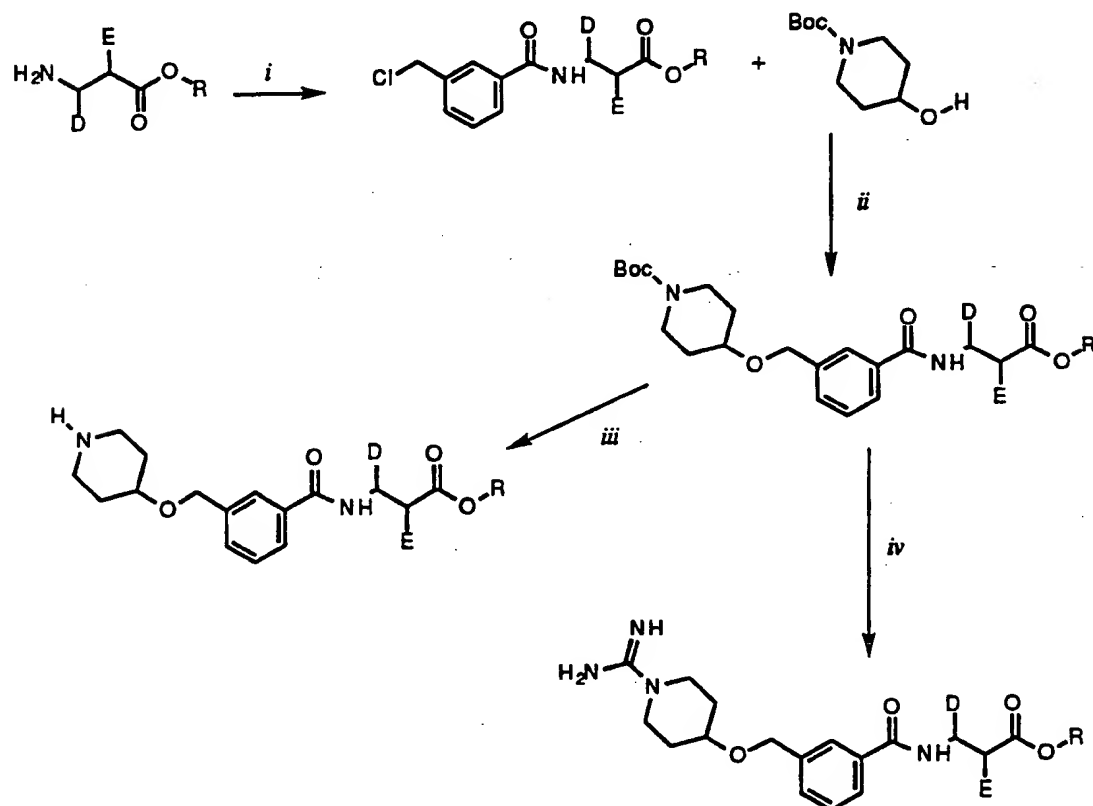
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When the compound of interest contains a piperidine or a *N*-amidinopiperidine connected to the central phenyl

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ring (V in Formula I) by a $(\text{CH}_2)_n\text{-O-CH}_2$ linking group, the structure can be prepared as described in Scheme IX, in which $n = 0$. Examples in which n is one or greater can be prepared by analogous methods.

5

Scheme IX

Reaction conditions: *i*) 3-(chloromethyl)benzoyl chloride, triethylamine; *ii*) NaH or $\text{KN}(\text{SiMe}_3)_2$; *iii*) TFA, or 4M HCl/Dioxane; *iv*) 1) TFA, or 4M HCl/Dioxane, 2) S-ethylthiourea, Et_3N , or $\text{H}_2\text{N-C(=NH)-SO}_3\text{H}$ /DMAP.

10

In Scheme IX, the substituents E, R, and D correspond to R^9 , R^{16} , and R^8 , respectively, in the compounds of Formula I as described above.

15

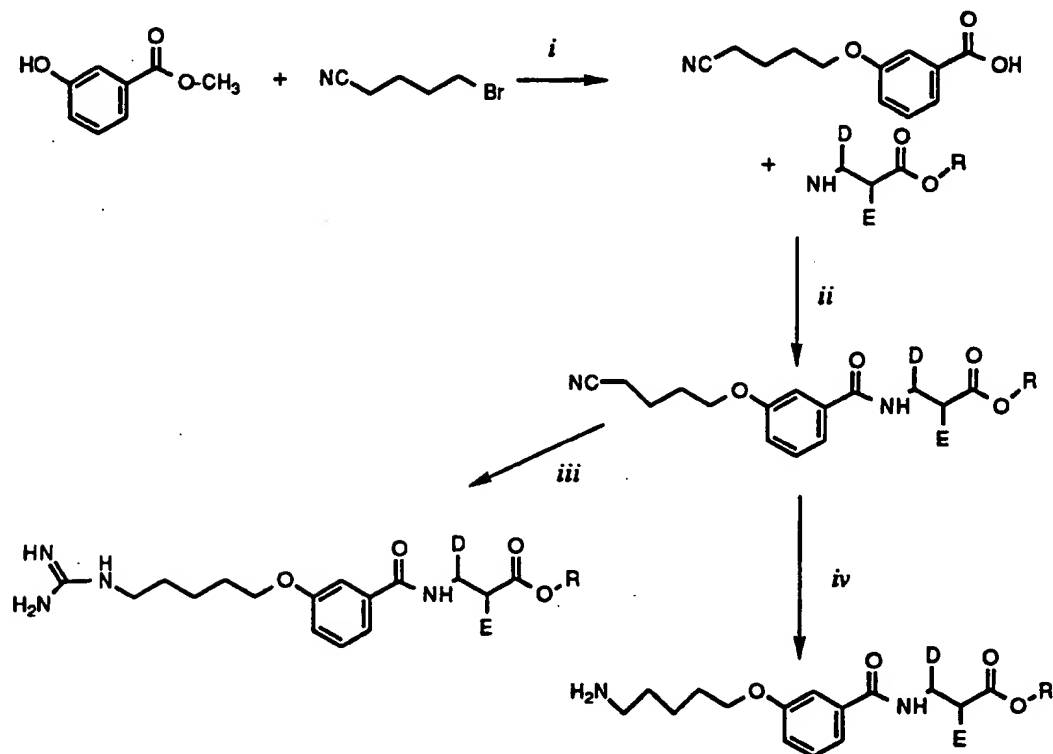
When the compound of interest contains an amine or a N-amidine-substituted amine connected to the central phenyl ring (V in Formula I) by a $(\text{CH}_2)_n\text{-O}$ linking group, the structure can be prepared as described in

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Scheme X, in which $n = 5$. Examples in which n is one to eight can be prepared by analogous methods.

Scheme X

5



Reaction conditions: *i*) 1) K_2CO_3 or NaH , 1) LiOH or LiOTM ; *ii*) DCC or $\text{TBTU}/\text{Et}_3\text{N}$; *iii*) 1) HCl , H_2 Pd/C or H_2/PtO_2 , 2) $\text{H}_2\text{N}-\text{C}(=\text{NH})\text{SO}_3\text{H}/\text{DMAP}$ or $\text{H}_2\text{N}-\text{C}(=\text{NH})-\text{S}-\text{Et}/\text{Et}_3\text{N}$; *iv*) HCl , H_2 Pd/C or HCl , H_2/PtO_2

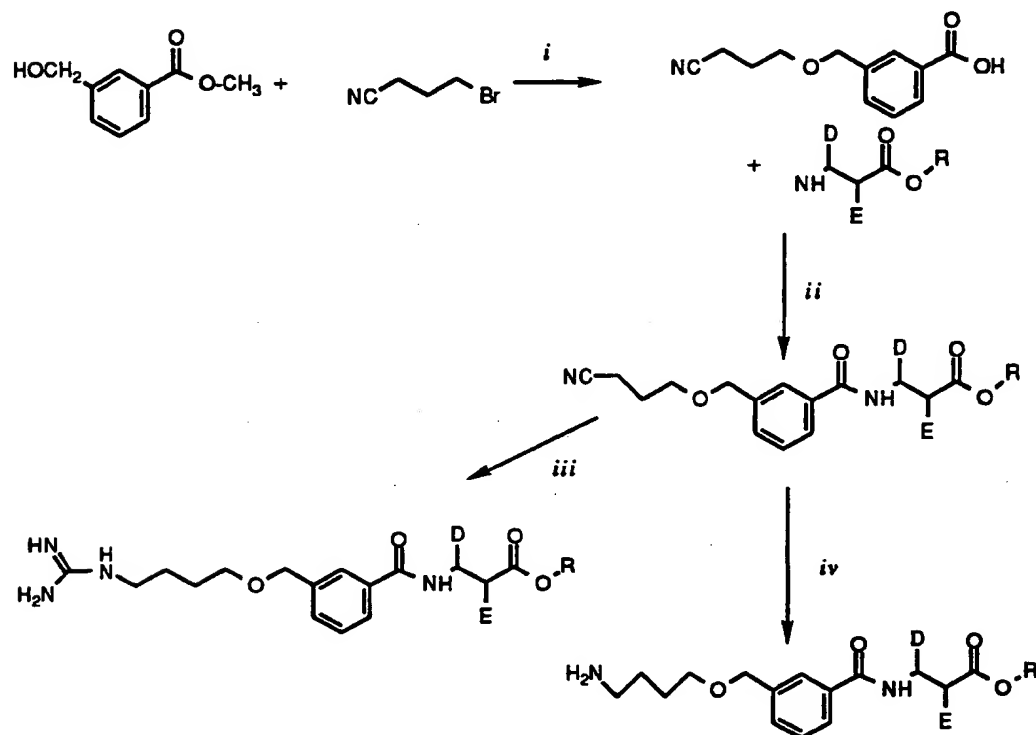
In Scheme IX, the substituents E, R, and D correspond to R^9 , R^{16} , and R^8 , respectively, in the compounds of Formula I described above.

Bromonitriles used in the above synthesis are generally commercially available, or can be prepared by treating a dibromide (in excess) with KCN at $50-100^\circ$ in DMSO.

When the compound of interest contains an amine or a N-amidine-substituted amine connected to the central phenyl ring (V in Formula I) by a $(\text{CH}_2)_n-\text{O}-\text{CH}_2$ linking

group, the structure can be prepared as described in Scheme XI, in which $n = 4$. Examples in which n is one to eight can be prepared by analogous methods.

5

Scheme XI

Reaction conditions: i) 1) $\text{KN}(\text{SiMe}_3)_2$, $\text{KOC}(\text{CH}_3)_3$ or NaH 2) LiOH or LiOTMS ; ii) DCC or $\text{TBTU/Et}_3\text{N}$; iii) 1) HCl , H_2 , Pd/C or H_2 , PtO_2 , 2) $\text{H}_2\text{N-C(=NH)-SO}_3\text{H/DMAP}$ or $\text{H}_2\text{N-C(=NH)-S-Et/Et}_3\text{N}$; iv) HCl , H_2 , Pd/C or H_2 , PtO_2

In Scheme XI, E, R, and D correspond to R^9 , R^{16} , and R^8 , respectively, in the compounds of Formula I.

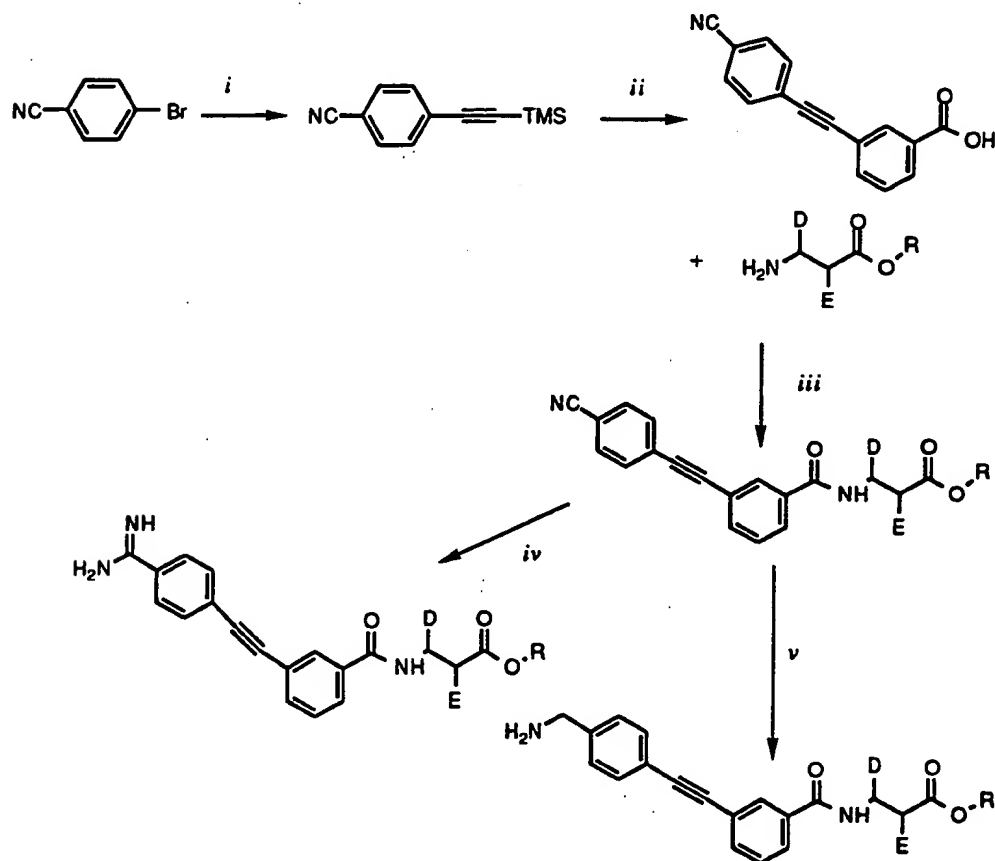
When the compound of interest contains an aryl amidine connected to the central phenyl ring (V in Formula I) by an acetylenic linking group the structure can be prepared as described in Scheme XII. Methods for the coupling of acetylenes to aryl bromides have been reviewed (Sandler and Karo, "Organic Functional Group Preparations" 2nd edition, Academic Press, INC, (1983) p. 90; Larock, "Comprehensive Organic Transformations"

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VDH Publishers, (1989), p. 302-305). Both the amidines and the corresponding aminomethyl compounds (Scheme XII) can be prepared from the central nitrile intermediate. The aminomethyl group can be N-alkylated by treatment of the primary amine with a ketone plus NaBH₃CN (Synthesis 135 (1975); Organic Preparations and Procedures, International 17, 317 (1983))

Scheme XII

10



Reagents: i) Trimethylsilyl-acetylene, Pd(Ph₃P)₃, CuI, Et₃N; ii) 1) TBAF, 2) Methyl-3-Bromobenzoate, Pd(Ph₃P)₃, CuI, Et₃N, 3) LiOH or LiOTMS; iii) DCC or TBTU/Et₃N iv) 1) HCl/methanol, 2) ammonia in methanol; or 1) H₂S/triethylamine, 2) MeI, 3) NH₃; v) 1) NaBH₄ CoCl₂ 2) HCl.

In Scheme XII, E, R, and D correspond to R⁹, R¹⁶, and R⁸, respectively, in the compounds of Formula I.

15

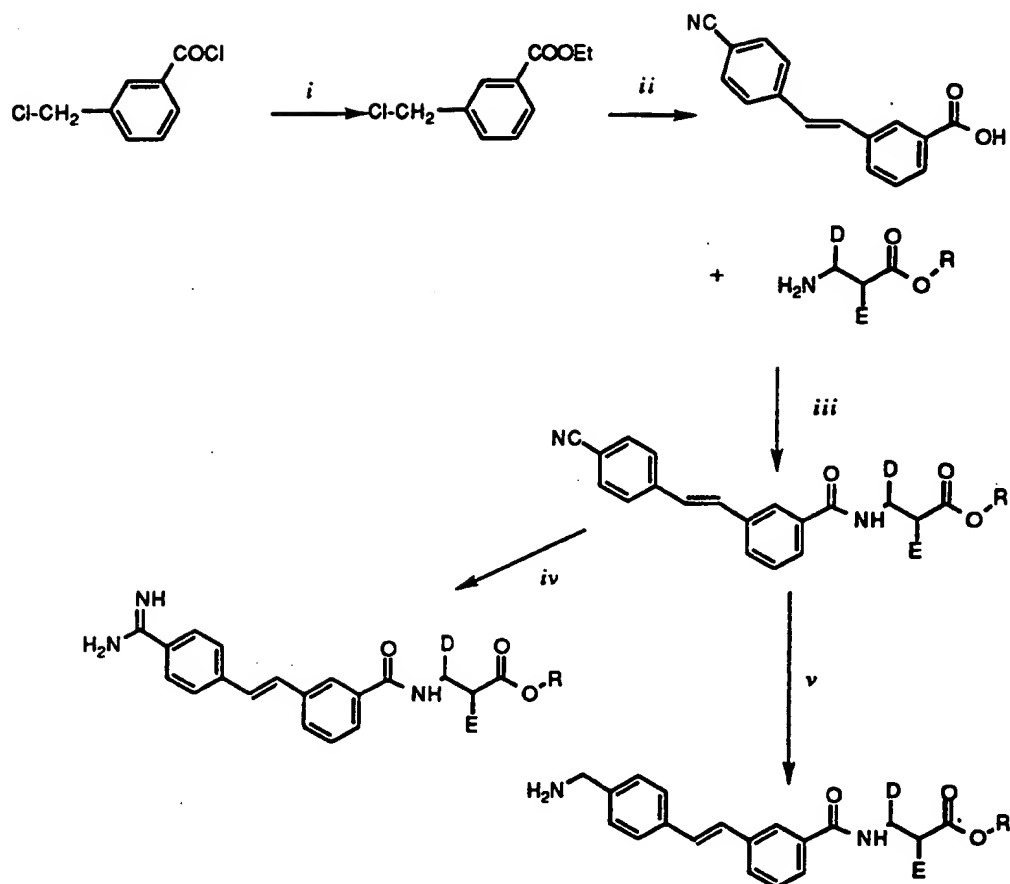
-62-

The acetylenic compounds described in Scheme XII can also be reduced to the corresponding cis alkenes by hydrogenation or hydroboration as described previously (Sandler and Karo, "Organic Functional Group Preparations" 2nd edition, Academic Press, INC, pp. 69-70).

When the compound of interest contains an aryl amidine connected to the central phenyl ring (V in Formula I) by a trans alkene linking group the structure can be prepared as described in Scheme XIII. Similar methods can be used to prepare the corresponding aminomethyl compounds (Scheme XIII). The aminomethyl group can be N-alkylated by treatment of the primary amine with a ketone plus NaBH_3CN (Synthesis 135 (1975); Organic Preparations and Procedures, International 17: 317 (1983)).

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Scheme XIII



Reagents: 1) EtOH; ii) 1) Ph_3P , 2) n-butyl lithium, 3) 4-cyanobenzaldehyde, 4) LiOH or LiOTMS; iii) DCC/HOBt or TBTU; iv) 1) HCl/methanol, 2) ammonia in methanol; or 1) H_2S /triethylamine, 2) MeI, 3) NH_3 ; v) NaBH_4 , CoCl_2 .

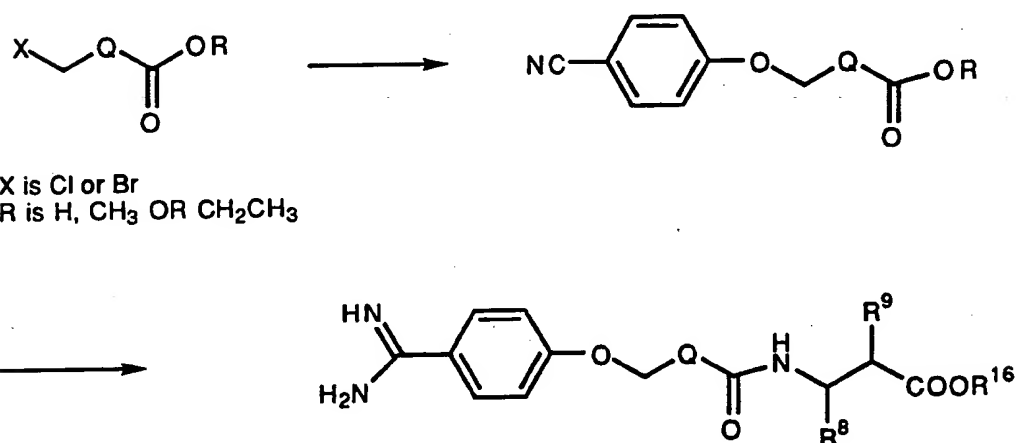
In Scheme XIII, the substituents E, R, and D correspond to R⁹, R¹⁶, and R⁸, respectively, in the compounds of Formula I.

The alkynes and alkenes described in Schemes XI and XII, respectively, can also be reduced to the corresponding alkanes by hydrogenation (Rylander, "Hydrogenation Methods" Academic Press, New York (1985), Chapter 3).

The central phenyl ring (V in Formula I) in the above compounds can be replaced with a variety of heterocycles (Q) by substitution of the appropriately functionalized heterocyclic starting material in Schemes I-XIII above. For example, compounds which have an aryl amidine connected to the central heterocyclic ring (Q) by an O-CH₂ linking group can be prepared as depicted in Scheme XIV.

10

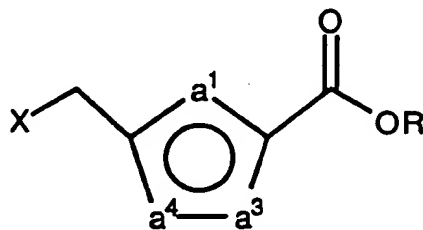
Scheme XIV



The heterocyclic starting materials used in Scheme XIV are prepared as described below.

1) Five-Membered Heterocyclics

Table 1 lists representative five-membered aromatic heterocyclic starting materials suitable for use in the preparation of compounds of the present invention.

Table 1. Five-membered Aromatic Heterocycles

5

R = H, Me or Et

X = Cl or Br

Q	a ¹	a ³	a ⁴
furan	O	CH	CH
furan	CH	CH	O
furan	CH	O	CH
thiophene	S	CH	CH
thiophene	CH	S	CH
thiophene	CH	CH	S
imidazole	N(H)	N(H)	CH
imidazole	N(H)	CH	N(H)
pyrrole	CH	CH	NH
pyrrole	NH	CH	CH
pyrrole	CH	NH	CH
pyrazole	CH	N(H)	N(H)
1,2,4-triazole	N(H)	N(H)	N(H)
oxazole	N	O	CH
oxazole	O	CH	N
thiazole	S	N	CH
thiazole	S	CH	N
isoxazole	CH	N	O
isoxazole	CH	O	N

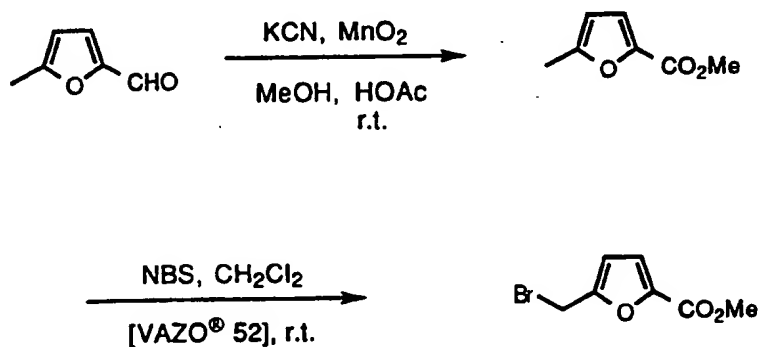
-66-

isothiazole	CH	N	S
isothiazole	CH	S	N
1,2,4-oxadiazole	N	N	O
1,2,4-oxadiazole	N	O	N
1,2,4-thiadiazole	N	N	S
1,2,4-thiadiazole	N	S	N
1,3,4-oxadiazole	O	N	N
1,3,4-thiadiazole	S	N	N

a) Furans

5 Synthesis of the 2,5-substituted linker (I)
could be accomplished starting with an oxidative
esterification (Corey, J. Amer. Chem. Soc., **1968**, **90**,
5616) of the commercially available 5-methylfurfural
(Scheme 1). The resulting methyl 5-methyl-2-furoic acid
10 is then carefully monobrominated with NBS at room
temperature, using VAZO[®] 52 as the initiator.

Scheme XVa

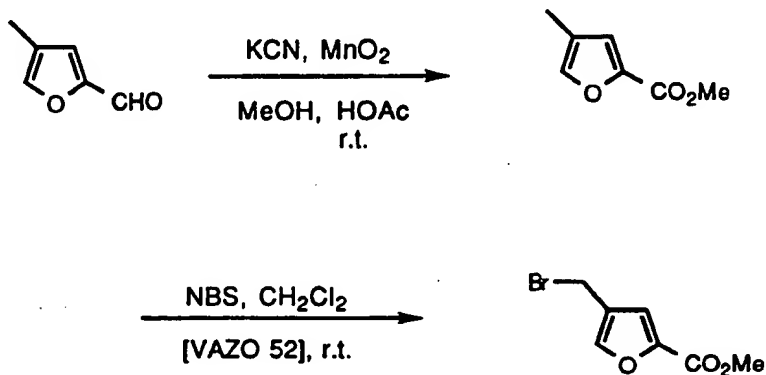


-67-

Synthesis of the corresponding 2,4-substituted isomer could be accomplished by using a similar approach starting with 4-methylfurfural (Chadwick, J. Chem. Soc., Perkin Trans. I, **1973**, 2327, 2329) as shown in Scheme

5 XVb.

Scheme XVb

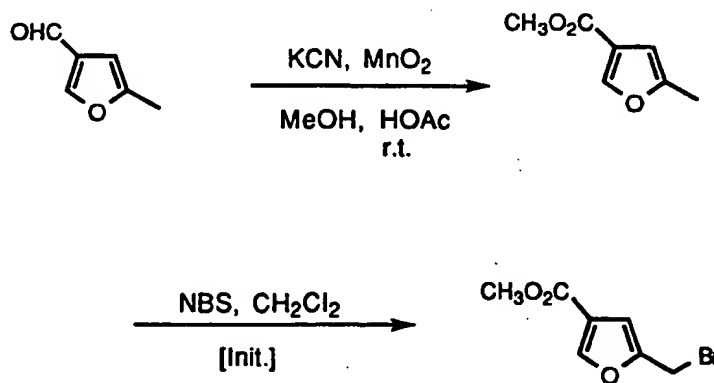


10

Analogously, the 3,5-isomeric furan can be prepared starting from 2-methyl-4-furaldehyde (Kotsuki, Chem. Lett. **1983**, 7, 1007) using the same strategy (Scheme XVc).

15

Scheme XVc



20

b) Thiophenes

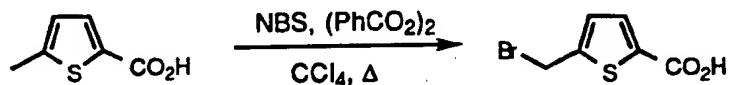
Synthesis of 5-bromomethyl-2-thiophenecarboxylic acid hydrochloride can be accomplished starting from 5-

-68-

methyl-2-thiophenecarboxylic acid (Rinker, Recl. Trav. Chim. Pays Bas, **1933**, 52, 538, 546; Paal, Chem. Ber. **1885**, 18, 2253) using the same general strategy described above for the furan linkers, as shown by

5 Scheme XVI.

Scheme XVI



10

Access to the 2,4- and 3,5- linker species may be gained through a common starting material, 3-bromo-5-methylthiophene (Gronowitz, Holm, Acta. Chem. Scand. (B), **1976**, 36, 505; Gronowitz, Adv. Het. Chem., **1963**, 1, 1).

15

Thus, as shown by Scheme XVIa, oxidation of the methyl group to the carboxylic acid, followed by its protection as the oxazoline (Meyers, Tetrahedron Lett., **1989**, 3303), lithiation of the bromide followed by

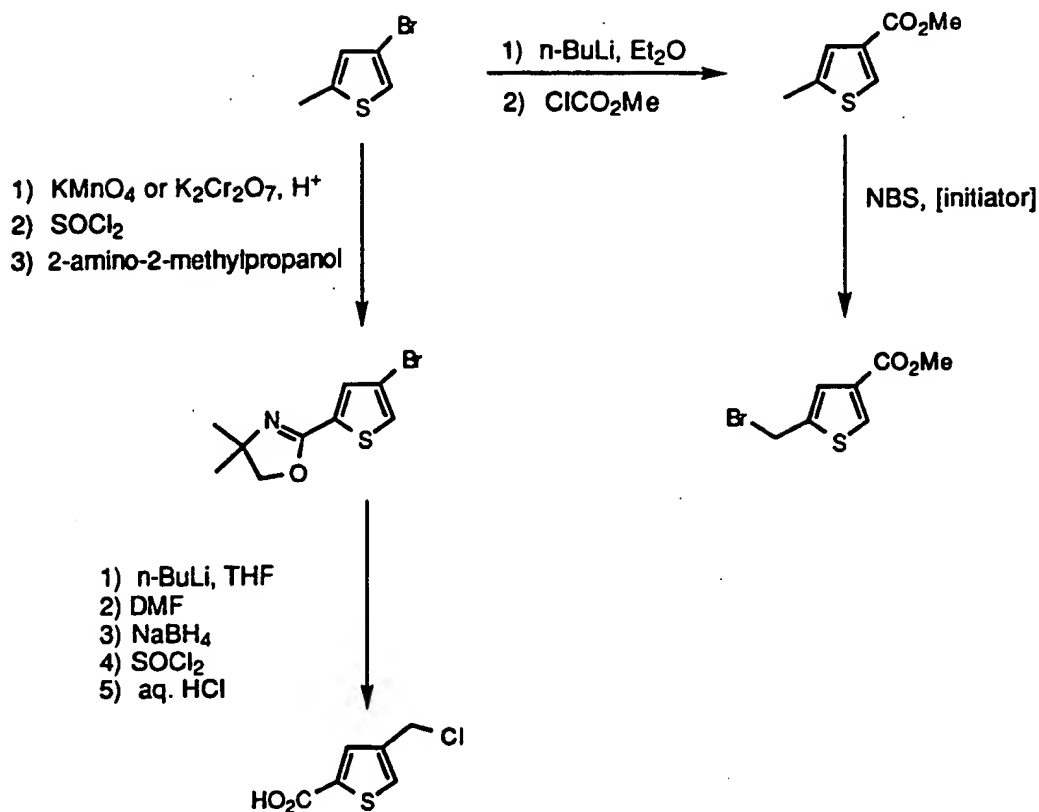
20 formylation with DMF, reduction to the alcohol, conversion to the chloromethyl group, and finally acid deprotection leads to 3-(chloromethyl)thiophene-5-carboxylic acid.

Alternatively, initial lithiation of 3-bromo-5-methylthiophene followed by capture with methyl chloroformate gives methyl 5-methylthiophene-3-carboxylate. Free-radical bromination of the methyl group provides 5-(bromomethyl)thiophene-3-carboxylic acid.

30

Scheme XVIa

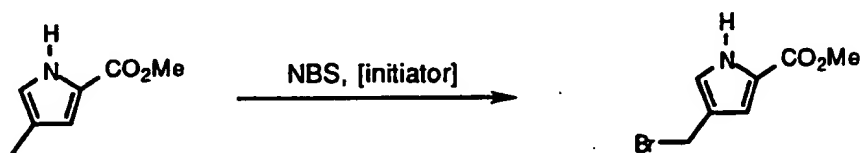
-69-

d) Pyrroles

- 5 Synthesis of methyl 4-(bromomethyl)pyrrole-2-carboxylate hydrochloride is prepared from methyl 4-methylpyrrole-2-carboxylate (Rapoport, J. Org. Chem., 1964, 29, 2727) as illustrated in Scheme XVII.

10

Scheme XVII



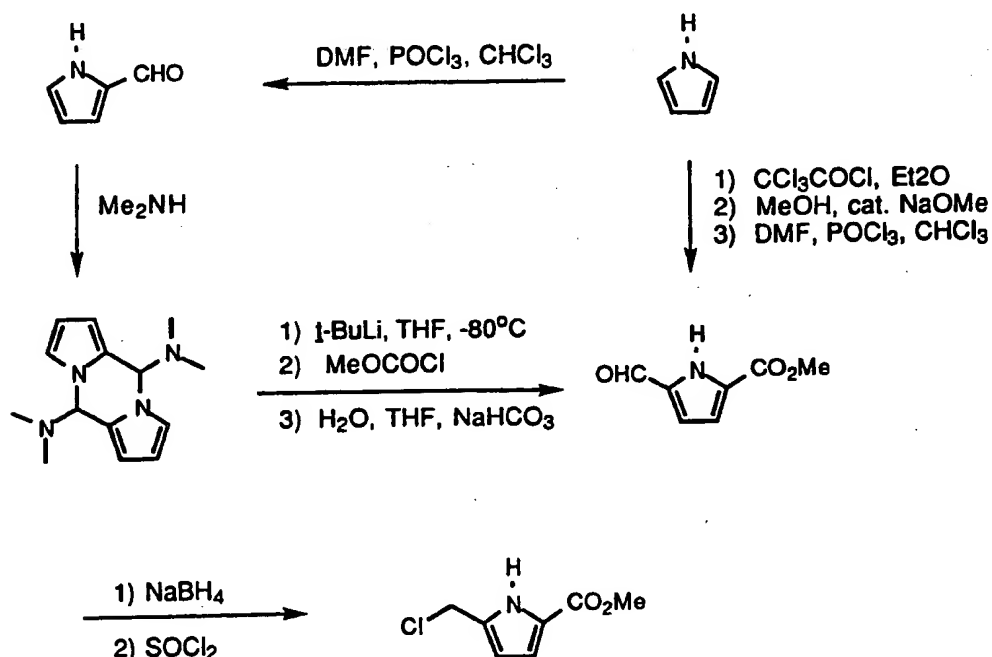
- 15 Preparation of methyl 5-(chloromethyl)pyrrole-2-carboxylate can be accomplished by the approach shown in Scheme XVIIa. A three-step conversion of pyrrole into methyl 5-formylpyrrole-2-carboxylate has been described (Org. Syn., Coll Vol. 4, 1963, p831). Alternatively,

-70-

Muchowski (Tetrahedron Lett., **1988**, **29**, 777) has described the bis(dimethylamino)azafulvene dimer resulting from treatment of 2-formylpyrrole with dimethylamine. Such species may be lithiated at low temperatures and captured with a variety of electrophiles, including methyl chloroformate, to also give methyl 5-formylpyrrole-2-carboxylate. The aldehyde group is then reduced to the alcohol which is further converted to the chloromethyl compound.

10

Scheme XVIIa

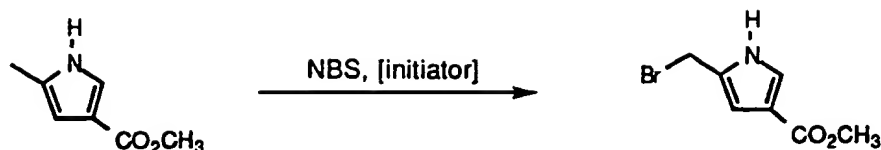


15 The third possible pyrrole starting material, methyl 5-(bromomethyl)pyrrole-3-carboxylate can be prepared according to Scheme XVIIb from methyl 5-methylpyrrole-3-carboxylate (Jones, J. Amer. Chem. Soc., **1955**, **77**, 4069, 4072) by bromination as previously

20 described above.

Scheme XVIIb

-71-

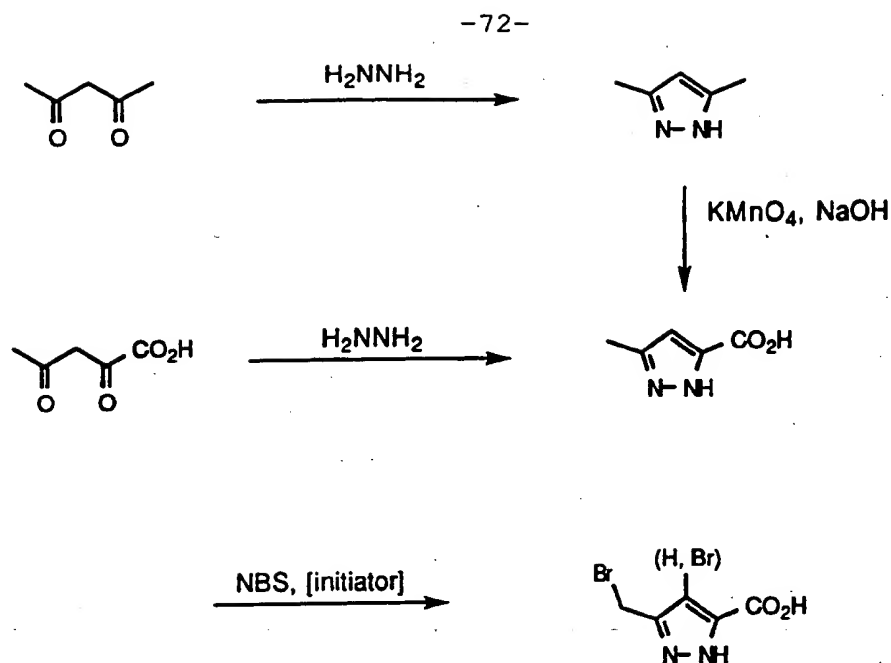
e) Pyrazole

5 Preparation of 5-(bromomethyl)pyrazole-3-carboxylic acid may be approached by the methods outlined in Scheme XVIII. Treatment of acetylacetone with hydrazine followed by selective oxidation of one of the two methyl groups of the resulting 3,5-dimethylpyrazole gives 5-methyl-pyrazole-3-carboxylic acid (Rothenburg, Chem. Ber., 1894, 27, 1097). Alternatively, this compound
10 may be prepared in one step by treatment of commercially available 2,4-dioxovaleric acid with hydrazine. The methyl group may then be converted to bromomethyl as
15 previously described.

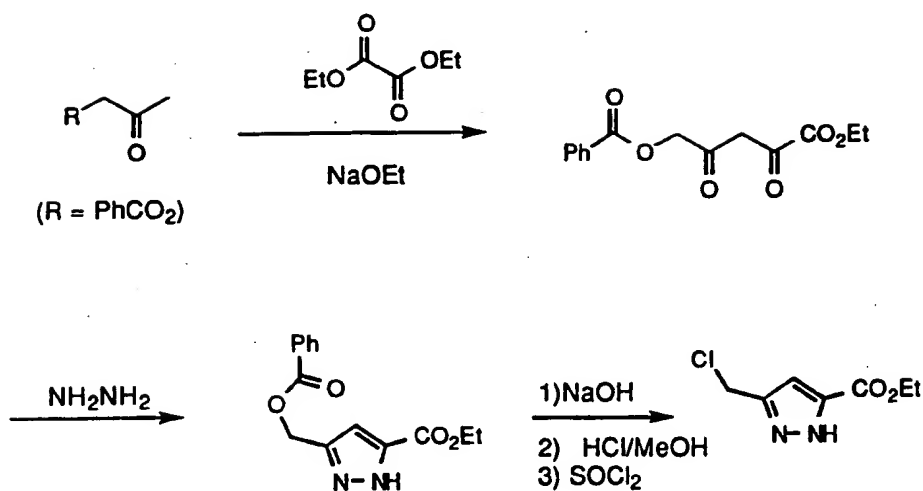
Alternatively, in the event of unwanted ring bromination during treatment with NBS, one may make use of ethyl 5-(benzoyloxy)-2,4-dioxo-valerate (Tschesche, Chem. Ber., 1958, 91, 2074, 2079) to prepare an
20 hydroxymethyl-substituted pyrazole intermediate which may then be transformed into an chloromethyl group by standard methods (Scheme XVIIIa).

Scheme XVIII

25



Scheme XVIIIa



5

f) 1,2,4-Triazole

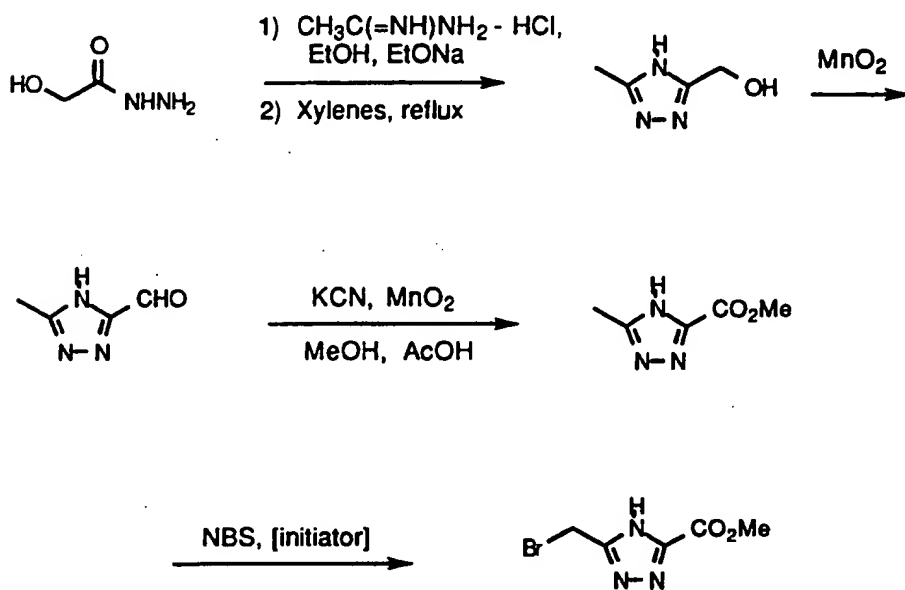
Synthesis of methyl 5-(bromomethyl)-1,2,4-triazole-3-carboxylate can be accomplished using the approach shown in Scheme XIX. The key intermediate, 3-(hydroxymethyl)-5-methyl-1,2,4-triazole, can be prepared according to the method of Francis (Tetrahedron Lett., **1987**, **28**, 5133) whereby hydroxyacetylhydrazide is condensed with acetamidine under base catalyzed

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-73-

conditions followed by thermolytic ring closure. The synthesis then proceeds in a similar fashion to some of the previously described linkers above in which the aldehyde is oxidatively esterified using Corey's
 5 procedure and the methyl group converted to bromomethyl as described above.

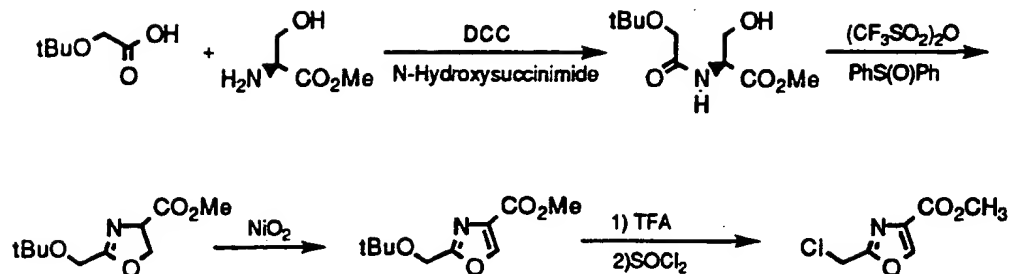
Scheme XIX

g) Oxazoles and Oxazolines

Yokokawa (Synthetic Lett., 1992, 2, 153) has
 15 recently described the preparation and cyclization of N-acylserine ester derivatives to give 2-substituted-4,5-dihydrooxazole-4-carboxylate esters which, after oxidation, give the corresponding 2-substituted-oxazole-4-carboxylate esters. By inference, N-acylation of
 20 serine methyl ester with t-butoxyacetic acid, followed by cyclization, oxidation, deprotection and conversion to the chloride by standard methods should give methyl 2-(chloromethyl)oxazole-4-carboxylate, as outlined in Scheme XX below. Elimination of the oxidation step
 25 will give the corresponding oxazoline.

-74-

Scheme XX

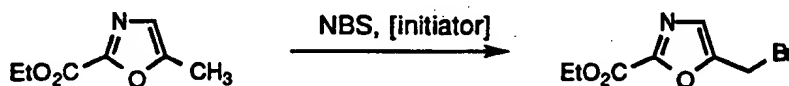


5

Tanimoto (Chem. Pharm. Bull., **1984**, 32, 1032) has reported the synthesis of ethyl 5-methyloxazole-2-carboxylate. The transformation of the methyl group to the bromomethyl, as previously described above, should lead to the ethyl 5-(bromomethyl)-2-carboxylate linker, as shown in Scheme XXa.

10

Scheme XXa



15

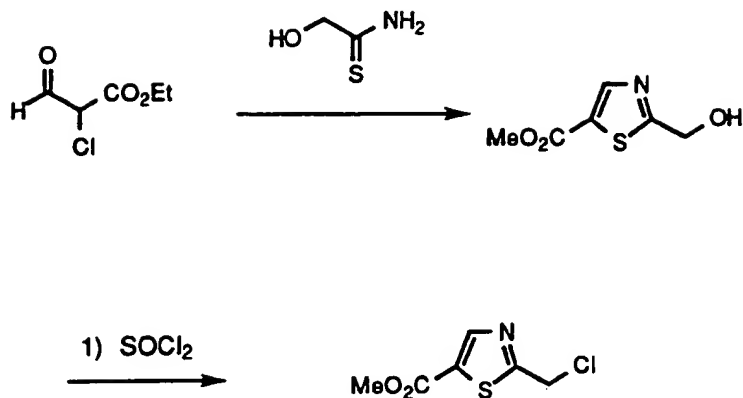
h) Thiazoles

Synthesis of ethyl 2-(hydroxymethyl)thiazole-5-carboxylate (and the corresponding carboxylic acid) has been reported (Poittevin, Hardy; Fr. Pat. DE2548505, [1976]). As illustrated in Scheme XXI below, further transformation of the hydroxymethyl group to chloromethyl as previously described should provide the 2-(chloromethyl)thiazole-5-carboxylic acid linker.

25

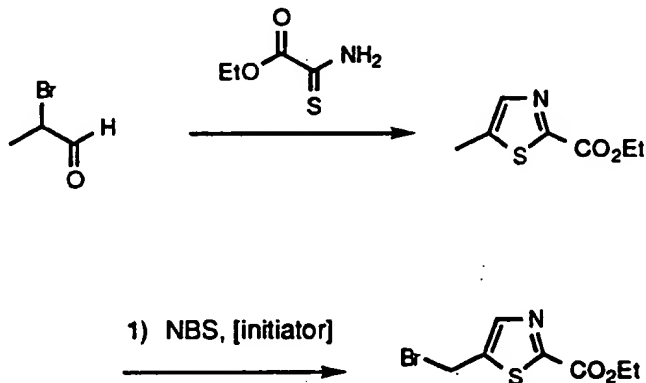
-75-

Scheme XXI



5 Synthesis of ethyl 5-methylthiazole-2-carboxylate
 has been accomplished by condensation of 2-
 bromopropionaldehyde with ethyl thiooxalamide
 (Erlenmeyer, Schmidt, Helv. Chim. Acta., 1946, 29,
 1957). As shown in Scheme XXIIa, further transformation
 10 of the methyl group into a bromomethyl, provides 5-
 (bromomethyl)thiazole-2-carboxylic acid.

Scheme XXIIa



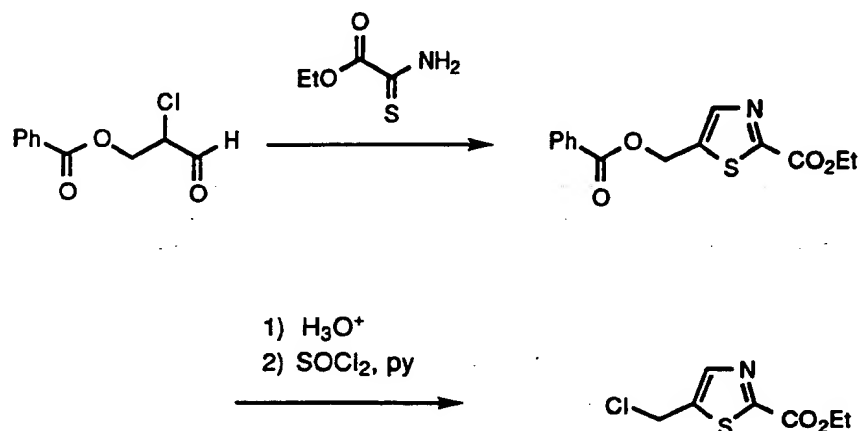
15

In the event of undesired ring bromination in the
 above scheme, one may make use of 2-chloro-3-
 (benzoyloxy)propionaldehyde (Hartman, Theory Pract.
 20 Affinity Tech. [Int. Symp.], 1978, 113) instead of 2-
 bromopropionaldehyde. Following comparable formation of
 the thiazole ring system, selective hydrolysis of the

-76-

benzoate ester and conversion of hydroxymethyl to chloromethyl as described above, (Scheme XXIb). Related known propionaldehyde derivatives such as 2-bromo-3-acetoxypropionaldehyde and 2-bromo-3-methoxypropionaldehyde may also serve as useful inroads to this series of thiazole compounds.

Scheme XXIb



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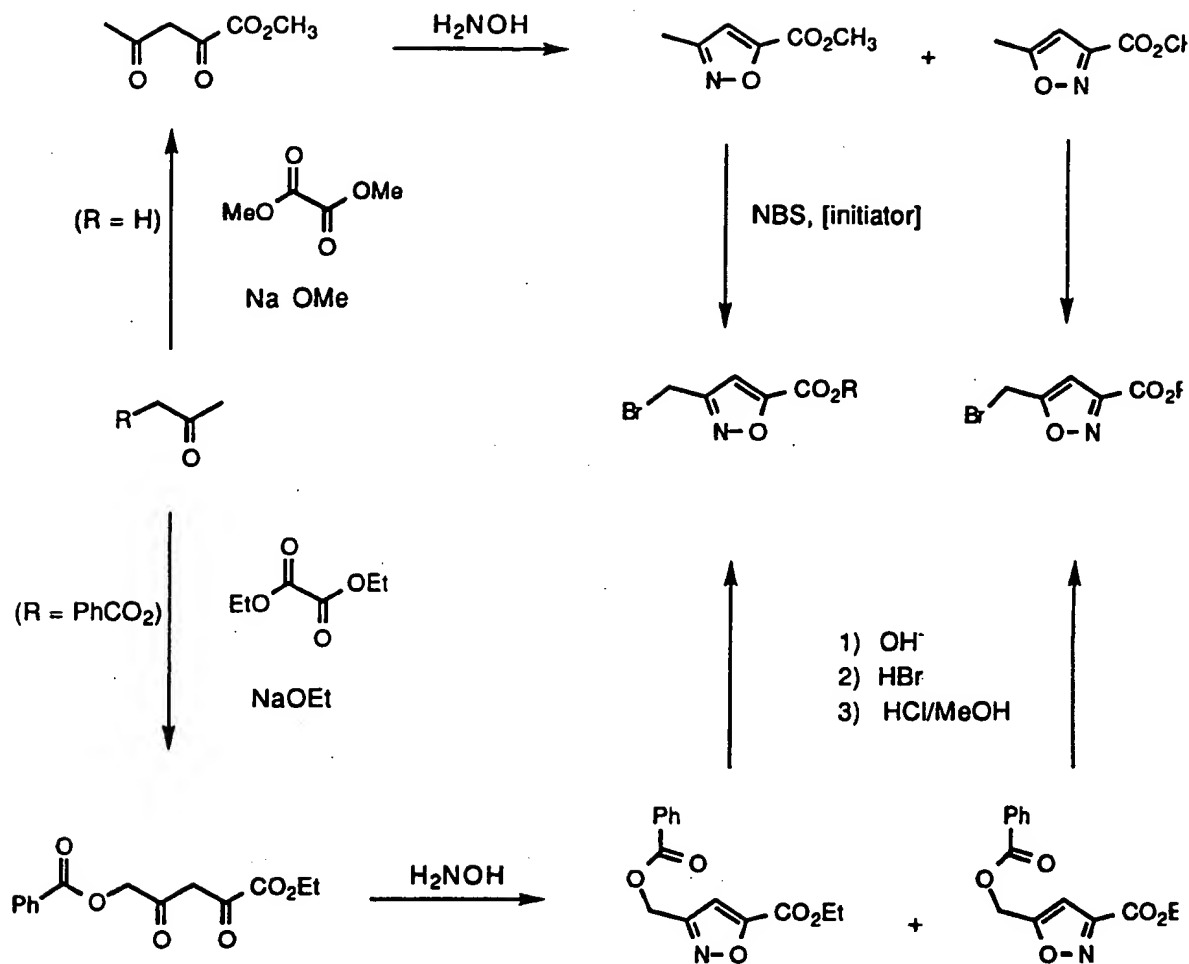
i) Isoxazoles and Isothiazoles

Analogous to the preparation of the pyrazole linker described above, an appropriate ester of 2,4-dioxovaleric acid (or the commercially available carboxylic acid itself) may be condensed with hydroxylamine to give, in this case, a mixture of the isomeric 3,5-disubstituted isoxazoles. Following separation of these isomers, the methyl group is converted to the bromomethyl as previously described. Again, as with the pyrazole case, in the event of unwanted ring bromination during treatment with NBS, one may instead start the synthesis using ethyl 5-(benzoyloxy)-2,4-dioxovalerate (Tschesche, Chem. Ber., **1958**, 91, 2074, 2079). See Scheme XXII

25

Scheme XXII

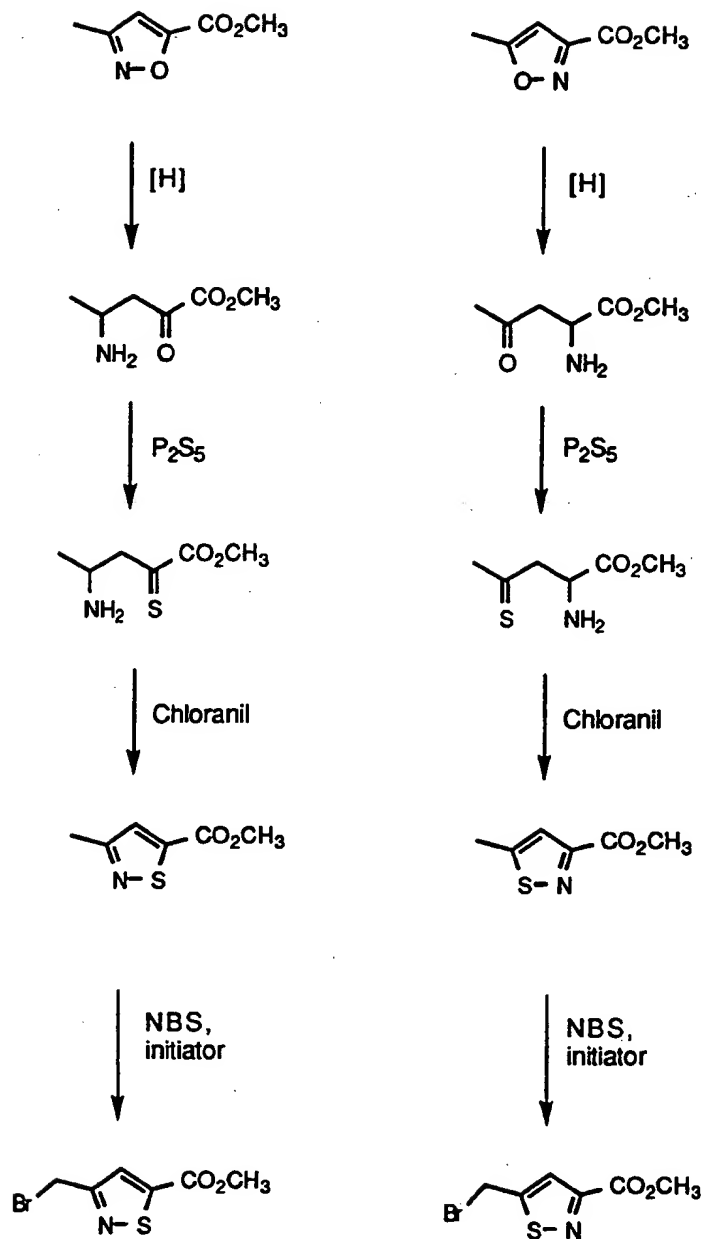
-77-



The corresponding isothiazoles can be prepared from their oxygen congeners via a three step process involving reductive ring opening, replacement of oxygen by sulfur using phosphorus pentasulfide, and oxidative ring closure (Newkome and Paudler, "Contemporary Heterocyclic Chemistry", Wiley-Interscience, N.Y., 1982; p41). Scheme XXIIa illustrates the approach.

-78-

Scheme XXIIa



5

j) Oxadiazoles and Thiadiazoles

The transformation of 3,5-dimethyl-1,2,4-oxadiazole to 3-oximino-5-methyl-1,2,4-oxadiazole has been described (Bedford, *J. Med. Chem.*, **1986**, **29**, 2174). As further illustrated in Scheme XXIII, oxidative

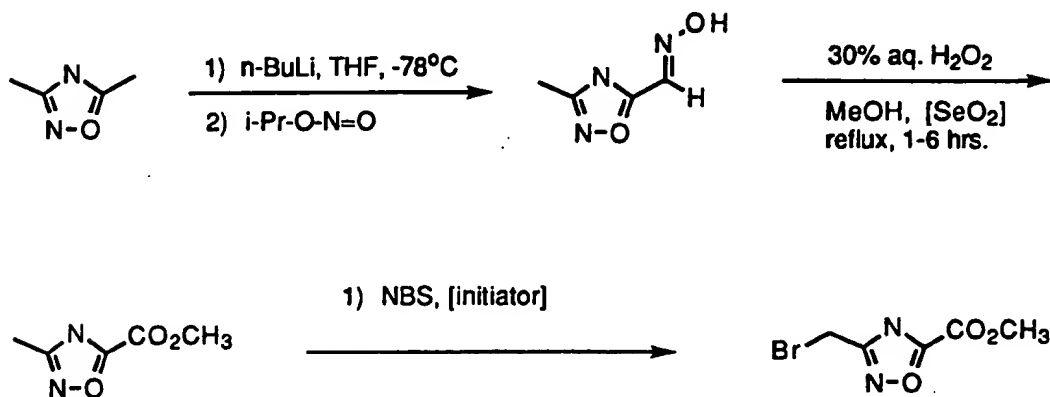
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-79-

esterification of this oxime according to Said (Synth. Commun., **1992**, **22**, 1851) leads to the corresponding ester. Conversion of methyl to chloromethyl as described above gives the desired chloroester.

5

Scheme XXIII



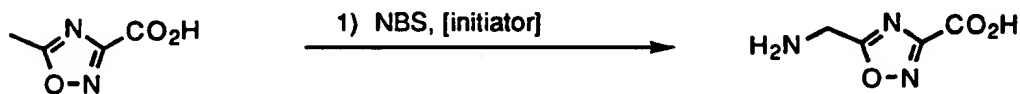
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In analogous fashion, 5-bromomethyl-1,2,4-oxadiazole-3-carboxylic acid may be prepared from the known precursor 5-methyl-1,2,4-oxadiazole-3-carboxylic acid (Ruccia, Ann. Chim. (Rome), **1968**, **58**, 4, 484),

15 according to Scheme XXIIIa. Prior esterification of the carboxylic acid of the starting material may be required to achieve efficient bromination in this case.

Scheme XXIIIa

20



25 The condensation of acetamidine with trichloromethyl-sulfonyl chloride to give 3-methyl-5-chloro-1,2,4-thiadiazole has been reported (Goerdeler, Chem. Ber., **1957**, **90**, 182, 184). Furthermore, MacLead (J. Med. Chem., **1990**, **33**, 2052) has demonstrated displacement of the chlorine with various carbon and

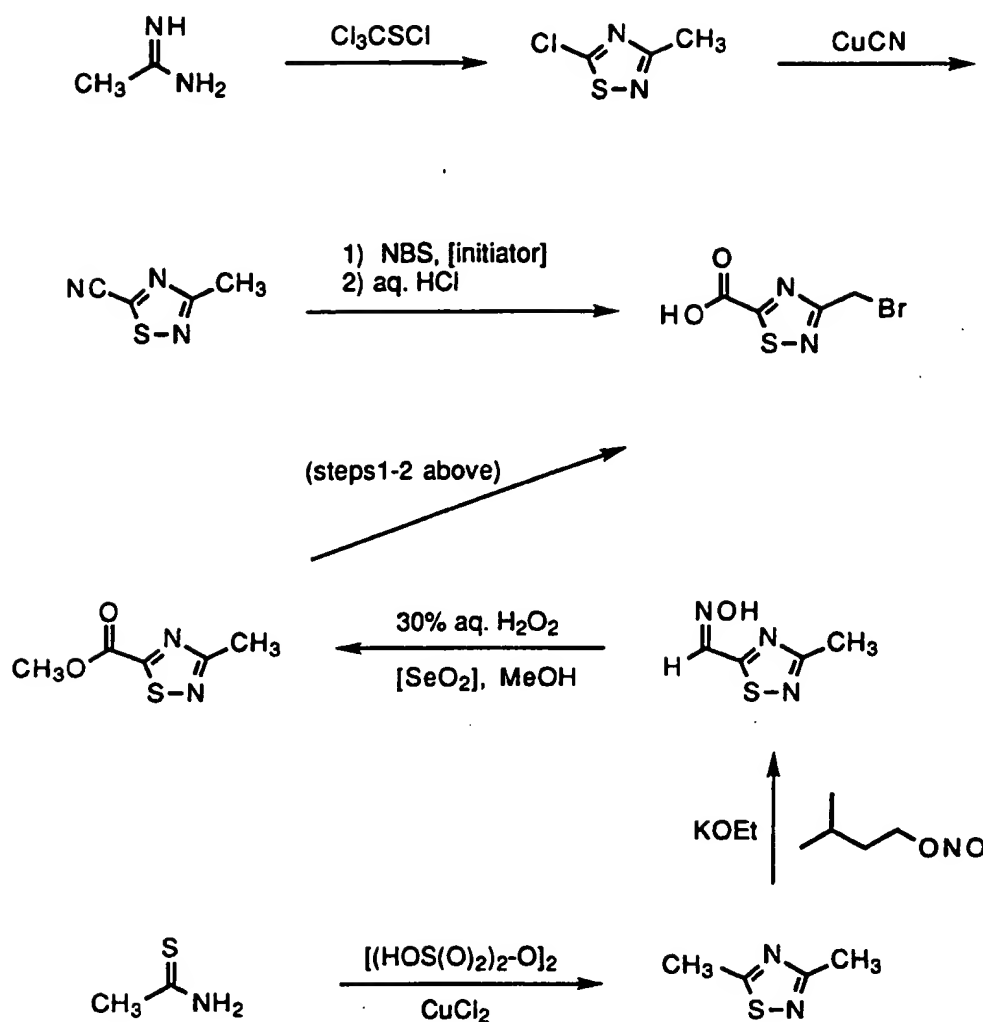
-80-

heteroatomic nucleophiles. Consequently, as shown in Scheme XXIIIb, displacement with cyanide followed by conversion of methyl to bromomethyl, and standard hydrolysis of the cyano group to the acid leads to 3-bromomethyl-5-carboxy-1,2,4-thiadiazole. In an alternative approach also shown in Scheme XXIIIb, 3,5-dimethyl-1,2,4-thiadiazole (Troyanski, Izv. Akad., Nauk. SSSR, Ser. Khim., 1986, 5, 1143) may be treated with isoamyl nitrite in the presence of potassium ethoxide to give 3-oximino-5-methyl-1,2,4-thiadiazole (Benschop, J. Med. Chem., 1979, 22, 1306). Oxidation of the oxime to the methyl ester (Said, Synth. Commun., 1992, 22, 1851) followed by transformation of methyl to bromomethyl as previously described also leads to the desired compound.

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-81-

Scheme XXIIIb

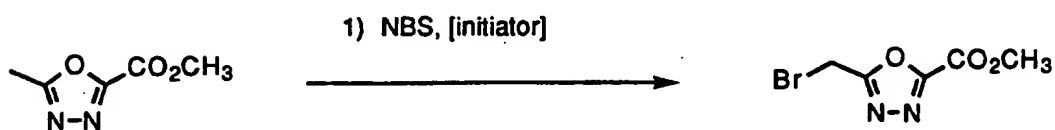


5

In Scheme XXIIIc, methyl 5-methyl-1,3,4-oxadiazole-2-carboxylate (Werber, Atti. Scand. Accad. Sci. Lett., Arti Palermo Parte 1, 1969-1970, 30, 175) is transformed to methyl 5-bromomethyl-1,3,4-oxadiazole-2-carboxylate using the methods described above.

10

Scheme XXIIIc

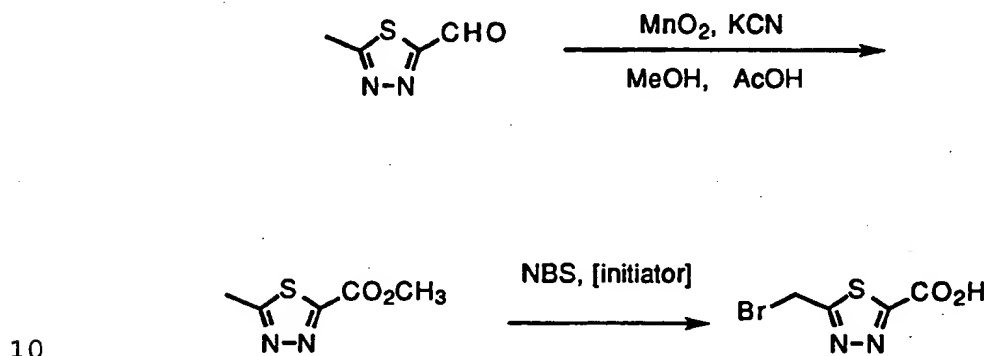


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-82-

Analogously, methyl 5-methyl-1,3,4-thiadiazole-2-carboxylate, prepared from the corresponding aldehyde precursor (Conway, EP125094 [1984]), is transformed by standard techniques to methyl 5-bromomethyl-1,3,4-thiadiazole-2-carboxylic acid as outlined in Scheme XXIIIId.

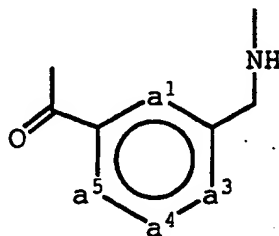
Scheme XXIIIc



2) Six-Membered Heterocycles

Table 2 lists representative six-membered aromatic heterocyclic starting materials suitable for use in the preparation of compounds of the present invention.

Table 2. Six-membered Heterocycles



<u>Class</u>	<u>a¹</u>	<u>a³</u>	<u>a⁴</u>	<u>a⁵</u>
pyridine	N	CH	CH	CH
pyridine	CH	CH	CH	N

-83-

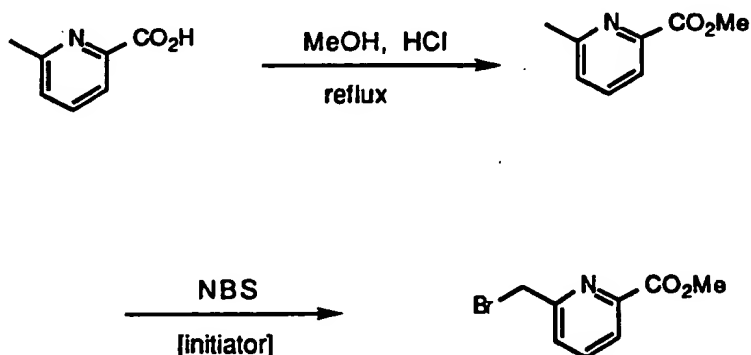
pyridine	CH	CH	N	CH
pyridine	CH	N	CH	CH
pyrazine	N	CH	N	CH
pyrimidine	N	CH	CH	N
pyrimidine	N	N	CH	CH
pyrimidine	CH	N	CH	N
pyridazine	CH	N	N	CH
pyridazine	CH	CH	N	N
1,2,3-triazine	CH	N	N	N
1,2,4-triazine	N	N	N	CH
1,2,4-triazine	N	CH	N	N

a) Pyridines

The 2,6-substituted linker may be prepared from commercially available 6-methylpicolinic acid (TCI, Japan) via Scheme XXIV. Esterification followed by previously discussed benzylic-type bromination, gives methyl 6-(bromomethyl)picolinate.

10

Scheme XXIV



Synthesis of ethyl 4-(bromomethyl)picolinate is depicted in Scheme XXIVa beginning with 4-picoline which

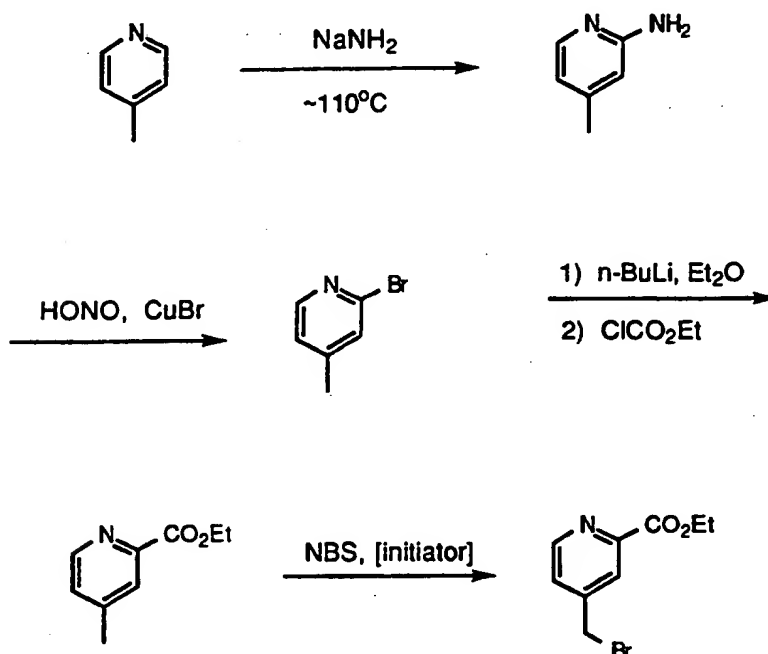
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-84-

is converted to 2-amino-4-picoline according to Tschitchibabin (J. Russ. Phys. Chem. Soc., **1914**, **46**, 1216). The amine in turn is subjected to Sandmeyer conditions to give the corresponding bromide. Halogen-metal exchange followed by quenching with ethyl chloroformate gives ethyl 4-methylpicolinate which is brominated using the conditions described above.

Scheme XIVA

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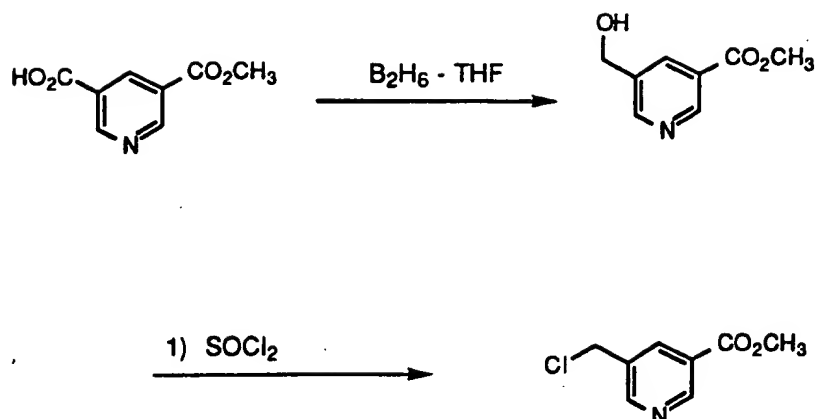


Selective reduction of the half acid/ester of methyl pyridine-3,5-dicarboxylate (Delarge, J. Pharm. Hely., **1969**, **44**, 637) with diborane to methyl 5-(hydroxymethyl)pyridine-3-carboxylate followed by conversion of hydroxymethyl to the corresponding chloride ethyl 5-(chloromethyl)-pyridine-3-carboxylate as illustrated in Scheme XIVb below.

20

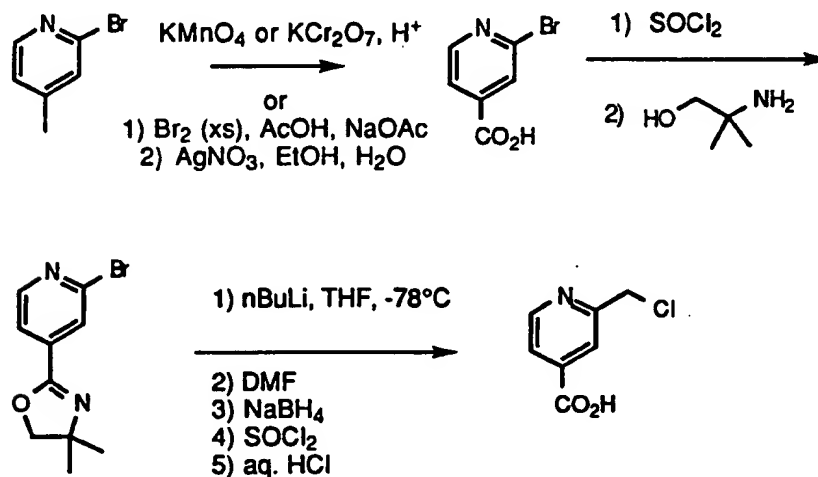
-85-

Scheme XIVb



- 5 Synthesis of ethyl 2-(chloromethyl)pyridine-4-carboxylate (Scheme XIVc) may be carried out starting with 2-bromo-4-methylpicoline. Halogen/metal exchange followed by quenching with DMF gives the formyl compound, which is further converted to the chloromethyl
- 10 compound by reduction and treatment with thionyl chloride. Acidic deprotection completes the sequence.

Scheme XIVc



15

b) Pyrazine

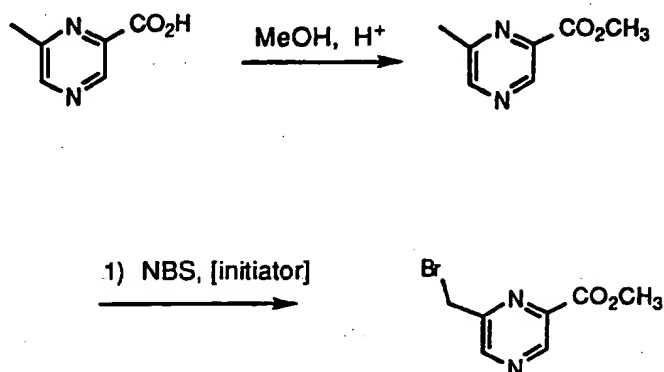
- The pyrazine linker may be prepared as shown in
- 20 Scheme XXV from 6-methylpyrazine-2-carboxylic acid

-86-

(Felder, Chem. Ber., **1967**, **100**, 2, 255; Spoerri, J. Amer. Chem. Soc., **1946**, **68**, 526) by esterification and conversion of the methyl group to a bromomethyl as previously described.

5

Scheme XXV



10

c) Pyrimidines

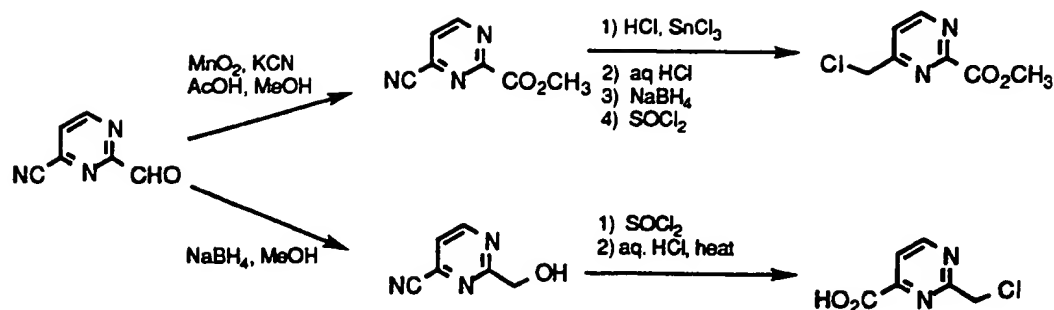
Scheme XXVI illustrates the preparation of either methyl 4-(chloromethyl)pyrimidine-2-carboxylate or 2-(chloromethyl)pyrimidine-4-carboxylic acid from the common intermediate 2-formyl-4-cyanopyrimidine (Stenck, EP335832, **1989**; CA: **112**, **21**, 197872w). For the former target, the aldehyde is oxidized to the ester (Corey procedure). Reduction of the nitrile to the aldehyde using the Stephen reaction (Mosettig, Org. React. 8, 219-257, 1954) borohydride reduction and reaction with thionyl chloride provides the desired ester.

Alternatively, selective reduction of the aldehyde to the hydroxymethyl group followed by its conversion to the chloride and hydrolysis of the nitrile gives the corresponding carboxylic acid.

25

Scheme XXVI

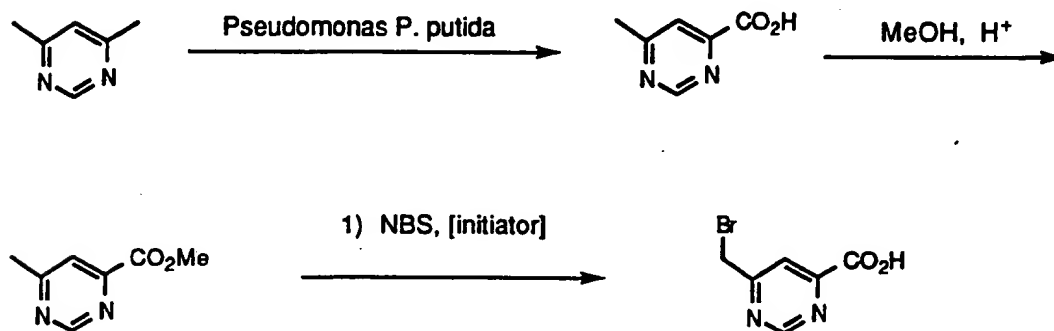
-87-



The third possible isomer in this series, methyl 6-(bromomethyl)-pyrimidine-3-carboxylate can be prepared from 6-methylpyrimidine-3-carboxylic acid (Kiener, EP 442430; CA: **116**, **7**, 57572f). Analogous to Scheme XXV (and others above), esterification followed by transformation of methyl to aminomethyl gives the desired linker, as shown in Scheme XXVla.

10

Scheme XXVla



15

d) Pyridazines

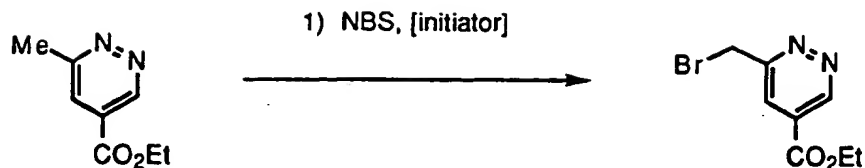
Ethyl 6-methylpyridazine-4-carboxylate has been described (Heinisch, *Tetrahedron*, **1985**, **41**, 1199; Turck, *C. R. Acad. Sci., Ser. C*, **1973**, **277**, 33).

20

Conversion of methyl to bromomethyl as previously described in several other schemes above, is illustrated in Scheme XXVII.

Scheme XXVII

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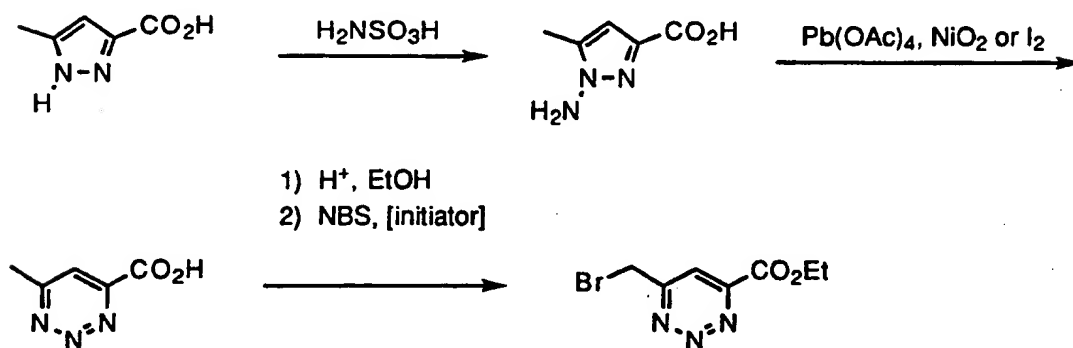
e) Triazines

5

Various methods have been described for the oxidative ring expansion of N-amino-pyrazoles to 1,2,3-triazines (Ohsawa, J. Chem. Soc., Chem. Commun., **1980**, 1182; Ibid, **1981**, 1174; Ohsawa, J. Org. Chem., **1985**, **50**, 5520; Ogata, Chem. Pharm. Bull., **1988**, **36**, 3838). Thus, N(1)-amino-5-methylpyrazole-3-carboxylic acid, obtained from the corresponding pyrazole described above and hydroxylamine-O-sulfonic acid (Neunhoeffer, Liebigs Ann. Chem., **1985**, **9**, 1732) is converted to 6-methyl-1,2,3-triazine-4-carboxylic acid according to Scheme XXVIII. Standard transformation of methyl to bromomethyl then provides ethyl 6-(bromomethyl)-1,2,3-triazine-4-carboxylate.

20

Scheme XXVIII



Rykowski has described the base-catalysed oximation of 3-methyl-1,2,4-triazine to give 3-methyl-5-oximino-1,2,4-triazine (Tetrahedron Lett., **1984**, 4795). Oxidative esterification of the oxime group according to Said (Synth. Commun., **1992**, **22**, 1851) followed by

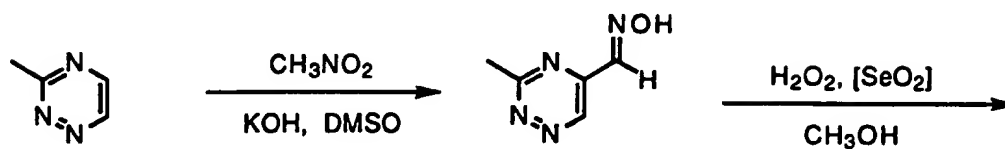
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-89-

bromination leads to methyl 3-bromomethyl-1,2,4-triazine-5-carboxylate. (Scheme XXVIIIa)

Scheme XXVIIIa

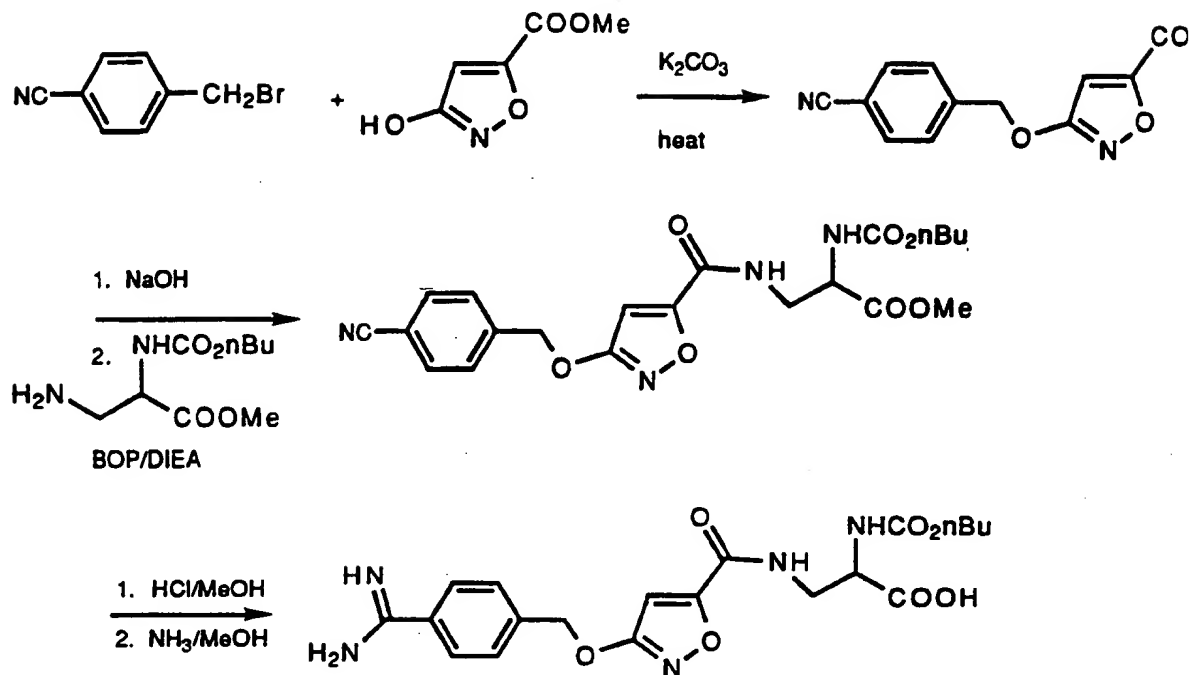
5



10 Compounds which have an aryl amidine connected to a central heterocyclic ring, for example isoxazole, by a $\text{CH}_2\text{-O}$ linking group can be prepared as shown in Scheme XIXa.

-90-

Scheme XIXa



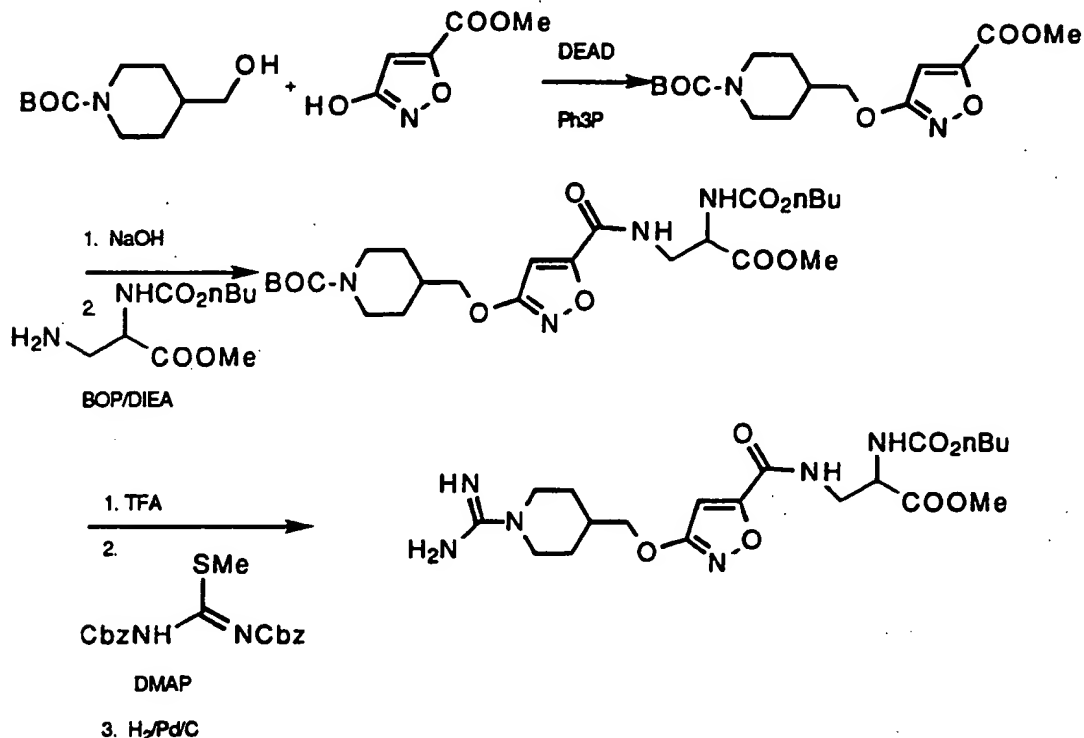
- 5 Alkylation of methyl 3-hydroxyisoxazole-5-carboxylate with 4-cyano- α -bromotoluene in the presence of a base, such as potassium carbonate, gives 3-[(4-cyanophenylmethoxy)-5-carboxymethylisoxazole.
- 10 Saponification of the ester and condensation with an appropriately substituted and protected diaminopropionic acid derivative gives the amide. Conversion of the nitrile to the amidine as described above and hydrolysis of the ester gives the desired product.
- 15 Scheme XIXb outlines the synthesis of the analogous compounds where R^1 is 4-(1-amidinopiperidinyl) instead of 4-amidinophenyl. After initial condensation of N-BOC-4-piperidinylcarbinol with methyl 3-hydroxyisoxazole-5-carboxylate under Mitsunobu
- 20 conditions, the intermediate ester is saponified and condensed with a 1,3-diaminopropionate using conditions described above. The piperidine nitrogen is deprotected and treated with N,N'-diCBz-S-methylisothiourea to give

-91-

a protected amidinopiperidine. Hydrogenation gives the amidinopiperidine compounds as the methyl esters.

Scheme XIXb

5



The detailed processes for preparing the compounds of Formula I are illustrated by the following Examples. It is, however, understood that this invention is not limited to the specific details of these examples. Melting points are uncorrected. Proton nuclear magnetic resonance spectra (^1H NMR) were measured in chloroform-d (CDCl_3) unless otherwise specified and the peaks are reported in parts per million (ppm) downfield from tetramethylsilane (TMS). The coupling patterns are reported as follows: s, singlet; d, doublet; t, triplet; q, quartet; qt, quintet; m, multiplet.

20

Example 2a

Methyl N²-t-butoxycarbonyl-N³-(3-(4-amidinophenylloxymethyl)benzoyl)-L-2,3-diaminopropionate.

-92-

TFA salt 2.0 g of 3-N-[3-(4-amidinophenyloxymethyl)benzoyl]-L-2,3-diaminopropionate (5.4 mmole) was dissolved in 30 ml solvent mixture (AcCN:H₂O:DMF 5:4:1). 1.25 ml di-t-butylidicarbonate (5.4 mmole) was added, then about 5 ml saturated NaHCO₃ solution was added, to bring the pH to 7.2. The solution was stirred 1-1/2 hours at room temperature. Analytical HPLC (Vydac C18 column, 1 ml/min., 0-50% B/50 min., A=99.9% H₂O/0.1% TFA, B=90% ACN/9.9% H₂O/0.1% TFA) showed the starting material was gone, and the appearance of a new peak. The reaction mixture was diluted 1:1 with 50% HOAc and purified directly on a Vydac prep C18 HPLC column, 10 ml/min., 22-42% B/40 min., detection at 290 nm. After lyophilization the overall yield was about 10% purified material. The identify of the material was confirmed by mass spec. (DCI) (Predicted MW 471.2; actual 471).

Example 6

Methyl N²-(3-phenylpropionyl)-N³-(3-(4-amidinophenyloxymethyl)benzoyl)-L-2,3-diaminopropionate TFA salt (XXXX). This compound was synthesized using the similar procedure as for XXXVIII from XXXVI (1 mmol, 520 mg), hydrocinnamoyl chloride (1 mmol, 0.15 mL) and NaHCO₃ (2.5 mmol, 200 mg). Purification on reversed phase HPLC gave 130 mg product. NMR (DMSO-d₆): δ 9.14 (s, 2H); 8.90 (s, 2H); 8.64 (t, 1H); 8.35 (d, 1H); 7.91 (s, 1H); 7.80 (d, 2H); 7.78 (d, 1H); 7.63 (d, 1H); 7.52 (t, 1H); 7.20 (m, 7H); 5.30 (s, 2H); 4.50 (m, 1H); 3.59 (s, 3H); 3.56 (m, 2H); 2.80 (m, 2H); 2.44 (m, 2H). N²-(3-phenylpropionyl)-N³-(3-(4-amidinophenyloxymethyl)benzoyl)-L-2,3-diaminopropionic acid TFA salt (XXXXI). XXXX (50 mg) was treated with 2 mL methanol and 1 mL 1 N NaOH for 1 hour and the solution was acidified with acetic acid. Purification on reversed phase HPLC gave 35 mg product.

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Example 9

Methyl N-2-1-butyloxycarbonyl-N³-(3-(4-
5 amidinophenylloxymethyl)benzoyl)-L-2,3-diaminopropionate
TFA salt (XXXVIII). To a solution containing XXXVI (4
mmol, 2.05 g) and NaHCO₃ (10 mmol, 0.8 g) in 5 mL water,
5mL acetonitrile and 2 mL DMF cooled in an ice bath was
added butyl chloroformate (4 mmol, 0.51 mL). The
10 solution was stirred for 1 hour, filtered, and acidified
with acetic acid. Purification on reversed phase HPLC
gave 450 mg product. NMR (DMSO-d₆): δ 9.15 (s, 2H);
8.92 (s, 2H); 8.62 (t, 1H); 7.92 (s, 1H); 7.81 (d, 2H);
7.79 (d, 1H); 7.62 (d, 1H); 7.57 (d, 1H); 7.50 (t, 1H);
15 7.24 (d, 2H); 5.30 (s, 2H); 4.28 (m, 1H); 3.95 (t, 2H);
3.60 (s, 3H); 3.59 (m, 2H); 1.50 (m, 2H); 1.30 (m, 2H);
0.86 (t, 3H).

N²-1-butyloxycarbonyl-N³-(3-(4-
amidinophenylloxymethyl)benzoyl)-L-2,3-diaminopropionic
20 acid TFA salt (XXXIX). XXXVIII (150 mg) was treated
with 3 mL methanol and 3 mL 1 N NaOH for 1 hour and the
solution was acidified with acetic acid. Purification
on reversed phase HPLC gave 110 mg product.

25 Example 9b

Valeric acid, N-hydroxysuccinimide ester N,N-
Dicyclohexylcarbodiimide (4.12g; 0.02mole) was added to
a solution of valeric acid (2.04g ; 0.02mole) and
30 hydroxysuccinimide(2.3g; 0.02mole) in 60ml of dioxane
with cooling. The reaction mixture was allowed to stand
overnight at room temperature. The formed
dicyclohexylurea was filtered and washed with dioxane.
The filtrate was evaporated under reduced pressure to
35 give crude N-hydroxysuccinimide ester of valeric acid as
an oil which was used without further purification.

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Ethyl N²-butyryl-N³-(3-(4-amidinophenyloxymethyl)benzoyl)-L-2,3-diaminopropionate, TFA salt A solution of the N-hydroxysuccinimide of valeric acid (0.24g; 0.001mole) in 4ml dimethylformamide was added to a solution of ethyl N³-[3-(4-Aminidophenyloxymethyl)benzoyl]-L-2,3-diaminopropionate (0.48g, 0.001mole) and N-methylmorpholine (0.13g; 0.001mole) in 4ml dimethylformamide. After 2 hrs the solvent was removed under vacu. The dry residue was dissolved in 10% acetic acid/water, purified using HPLC(Vydac C-18 prep column; program from 10% to 50% buffer 1% per min., 10ml per min. Buffer A: 99.9% water +0.1% TFA Buffer B: 90% Acetonitrile + 9.9 % water + 0.1% TFA) and lyophilized to give the title compound. (M+1)=455

15

Example 14

Methyl N²-1-butanesulfonyl-N³-Boc-L-2,3-diaminopropionate (XXX). To a solution of XXIII (3 mmol, 767 mg) in 10 mL THF was added 1-butanesulfonyl chloride (3 mmol, 0.393 mL) followed by triethylamine (7 mmol, 0.974 mL) and the solution was stirred at 50° C overnight and then at 60° C for 6 hours and concentrated. The residue was taken up in ethyl acetate and the solution was washed with 1% citric acid, brine, NaHCO₃ and brine, dried (MgSO₄), and concentrated. Crystallization from ether gave 570 mg (56%) product. NMR (DMSO-d₆): δ 7.66 (d, 1H); 6.92 (t, 1H); 4.04 (m, 1H); 3.64 (s, 3H); 3.21 (m, 2H); 2.96 (m, 2H); 1.61 (m, 2H); 1.37 (s, 9H); 1.36 (m, 2H); 0.88 (t, 3H).

Methyl N²-1-butanesulfonyl-L-2,3-diaminopropionate TFA salt (XXXI). XXX (1.68 mmol, 570 mg) was treated with 60% TFA in methylene chloride (5 mL) for 1 hour and the solution was concentrated. Yield 600 mg (100%). NMR (DMSO-d₆): δ 8.06 (b, 3H); 7.95 (d, 1H); 4.30 (m, 1H); 3.72 (s, 3H); 3.20 (m, 1H); 3.08 (m, 2H); 3.00 (m, 1H); 1.66 (m, 2H); 1.39 (m, 2H); 0.89 (t, 3H).

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Methyl N²-1-butanesulfonyl-N³-(3-chloromethylbenzoyl)-L-2,3-diaminopropionate (XXXII). This compound was synthesized using a similar procedure as for I from 3-chloromethylbenzoyl chloride (2 mmol, 284 mg), XXXI (2 mmol, 704 mg) and triethylamine (5 mmol, 0.70 mL). Purification on a silica gel column using ethyl acetate/hexane gave 490 mg (63%) crystalline product. NMR (DMSO-d₆): δ 8.63 (t, 1H); 7.90 (s, 1H); 7.82 (d, 1H); 7.79 (d, 1H); 7.61 (d, 1H); 7.50 (t, 1H); 4.82 (s, 2H); 4.23 (m, 1H); 3.64 (s, 3H); 3.57 (m, 2H); 2.95 (m, 2H); 1.60 (m, 2H); 1.28 (m, 2H); 0.80 (t, 3H).

Methyl N²-1-butanesulfonyl-N³-(3-(4-cyanophenyloxymethyl)benzoyl)-L-2,3-diaminopropionate (XXXIII). This compound was synthesized in a similar way as for II from XXXII (1.15 mmol, 450 mg), 4-cyanophenol (1.15 mmol, 137 mg) and potassium carbonate (2.3 mmol, 318 mg). Yield 470 mg (86%). NMR (DMSO-d₆): δ 8.64 (t, 1H); 7.94 (s, 1H); 7.80 (m, 4H); 7.64 (d, 1H); 7.52 (t, 1H); 7.20 (d, 2H); 5.26 (s, 2H); 4.24 (m, 1H); 3.64 (s, 3H); 3.58 (m, 2H); 2.95 (m, 2H); 1.60 (m, 2H); 1.27 (m, 2H); 0.80 (t, 3H).

Methyl N²-1-butanesulfonyl-N³-(3-(4-amidinophenyloxymethyl)benzoyl)-L-2,3-diaminopropionate TFA salt (XXXIV). This compound was synthesized from XXXIII (0.95 mmol, 450 mg) in a similar way as for XX. Yield 250 mg (43%). NMR (DMSO-d₆): δ 9.15 (s, 2H); 8.92 (s, 2H); 8.66 (t, 1H); 7.94 (s, 1H); 7.80 (m, 4H); 7.64 (d, 1H); 7.50 (t, 1H); 7.25 (d, 2H); 5.30 (s, 2H); 4.22 (m, 1H); 3.64 (s, 3H); 3.57 (m, 2H); 2.95 (m, 2H); 1.60 (m, 2H); 1.28 (m, 2H); 0.80 (t, 3H).

N²-1-butanesulfonyl-N³-(3-(4-amidinophenyloxymethyl)benzoyl)-2,3-diaminopropionic acid TFA salt (XXXV). This compound was synthesized by saponification of XXXIV (50 mg) with NaOH in methanol and purification on reversed phase HPLC. Yield 30 mg. ESI (M+H)⁺: Calcd. 477.2; Found 477.3.

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Example 16

Methyl N²-Cbz-N³-Boc-L-2,3-diaminopropionate (XXII). To a solution of V (13.9 mmol, 4 g) and di-tert-butyl dicarbonate (13.9 mmol, 3.03 g) in 30 mL THF cooled in an ice bath was added triethylamine (15 mmol, 2.1 mL) and the solution was stirred for 4 hours. Dilute citric acid solution was added followed by ethyl acetate. The organic layer was separated, washed with dilute citric acid, brine, NaHCO₃ and brine, dried (MgSO₄), and concentrated. Crystallization from ether-petroleum ether gave 4.68 g (96%) crystalline product. NMR (DMSO-d₆): δ 7.60 (d, 1H); 7.35 (m, 5H); 6.88 (t, 1H); 5.02 (s, 2H); 4.14 (m, 1H); 3.60 (s, 3H); 3.28 (m, 2H); 1.37 (s, 9H).

Methyl N³-Boc-L-2,3-diaminopropionate HCl salt (XXIII). A mixture of XXII (12.2 mmol, 4.32 g), concentrated HCl (14.7 mmol, 0.87 mL) and 10% Pd/C (432 mg) in 30 mL methanol was hydrogenated at atmospheric pressure for 4 hours. The catalyst was filtered off and the solution was concentrated. Ether was added and the solid was filtered, washed with ether to give 2.46 g (80%) product. NMR (DMSO-d₆): δ 8.55 (b, 3H); 7.13 (t, 1H); 3.96 (m, 1H); 3.70 (s, 3H); 3.44 (m, 2H); 1.38 (s, 9H).

Methyl N²-p-toluenesulfonyl-N³-Boc-L-2,3-diaminopropionate (XXIV). To a solution of XXIII (3 mmol, 767 mg) in 10 mL THF was added p-toluenesulfonyl chloride (3 mmol, 572 mg) followed by triethylamine (7 mmol, 0.98 mL) and the solution was stirred for 4 hours. Ethyl acetate was added and the solution was washed with dilute citric acid, brine, NaHCO₃ and brine, dried (MgSO₄), and concentrated. Crystallization from ether-petroleum ether gave 890 mg (79%) product. NMR (DMSO-d₆): δ 8.20 (d, 1H); 7.64 (d, 2H); 7.38 (d, 2H); 6.84 (t, 1H); 3.90 (m, 1H); 3.38 (s, 3H); 3.10 (m, 2H); 2.39 (s, 3H); 1.32 (s, 9H).

- Methyl N²-p-toluenesulfonyl-L-2,3-diaminopropionate TFA salt (XXV). XXIV (2.37 mmol, 880 mg) was treated with 10 mL 60% TFA in methylene chloride for 1 hour and the solution was concentrated. The residue was triturated with ether-petroleum ether to give 700 mg (76%) product. NMR (DMSO-d₆): δ 8.52 (d, 1H); 8.08 (b, 3H); 7.66 (d, 2H); 7.40 (d, 2H); 4.16 (m, 1H); 3.36 (s, 3H); 3.10 (m, 1H); 2.90 (m, 1H); 2.38 (s, 3H).
- Methyl N²-p-toluenesulfonyl-N³-(3-chloromethylbenzoyl)-L-2,3-diaminopropionate (XXVI). This compound was synthesized in a similar was as for I from 3-chloromethylbenzoyl chloride (1.5 mmol, 0.21 mL), XXV (1.6 mmol, 621 mg) and triethylamine (3.5 mmol, 0.49 mL). Yield 638 mg (100%). NMR (DMSO-d₆): δ 8.56 (t, 1H); 8.35 (d, 1H); 7.80 (s, 1H); 7.62 (m, 4H); 7.46 (t, 1H); 7.26 (d, 2H); 4.80 (s, 2H); 4.08 (m, 1H); 3.50 (m, 2H); 3.40 (s, 3H); 2.30 (s, 3H).
- Methyl N²-p-toluenesulfonyl-N³-(3-(4-cyanophenyloxymethyl)benzoyl)-L-2,3-diaminopropionate (XXVII). This compound was synthesized in a similar way as for II from XXVI (1.5 mmol, 637 mg), 4-cyanophenol (1.5 mmol, 179 mg) and potassium carbonate (3 mmol, 415 mg). Purification on a silica gel column using ethyl acetate/hexane gave 340 mg (45%) solid product. NMR (DMSO-d₆): δ 8.56 (t, 1H); 8.35 (d, 1H); 7.84 (s, 1H); 7.80 (d, 2H); 7.70 (d, 1H); 7.61 (m, 3H); 7.50 (t, 1H); 7.28 (d, 2H); 7.20 (d, 2H); 5.26 (s, 2H); 4.06 (m, 1H); 3.50 (m, 1H); 3.38 (m, 1H); 3.39 (s, 3H); 2.30 (s, 3H).
- Methyl N²-p-toluenesulfonyl-N³-(3-(4-amidinophenyloxymethyl)benzoyl)-L-2,3-diaminopropionate TFA salt (XXVIII). This compound was synthesized from XXVII (0.63 mmol, 320 mg) using the similar procedure as for XX. Purification on reversed phase HPLC gave 125 mg (31%) product. NMR (DMSO-d₆): δ 9.14 (s, 2H); 8.94 (s, 2H); 8.59 (t, 1H); 8.35 (d, 1H); 7.86 (s, 1H); 7.81 (d, 2H); 7.70 (d, 1H); 7.60 (m, 3H); 7.50 (t, 1H); 7.28 (d,

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2H); 7.25 (d, 2H); 5.30 (s, 2H); 4.08 (m, 1H); 3.44 (m, 2H); 3.38 (s, 3H); 2.30 (s, 3H).

N²-p-toluenesulfonyl-N³-(3-(4-

amidinophenyloxymethyl)benzoyl)-L-2,3-diaminopropionic

- 5 acid TFA salt (XXIX). This compound was synthesized by saponification of XXVIII with NaOH in methanol and then purification on reversed phase HPLC. ESI (M+H)⁺: Calcd. 511.2; Found 511.2.

10

Example 19a

Methyl-N²-nicotinoyl-N³-(3-(4-

amidinophenyloxymethyl)benzoyl)-L-2,3-diaminopropionate.

- 15 TFA salt Methyl-N²-tertbutyloxycarbonyl-N³-(3-(4-amidinophenyloxymethyl)-benzoyl)-L-2,3-diaminopropionate (25 mg, 0.043 mmol) was dissolved in 300 mL of trifluoroacetic acid and stirred at room temperature for 5 minutes. Cold diethyl ether was added to the reaction mixture and a white precipitate formed. The supernatant was removed and the precipitate was washed with diethyl ether and dried. To this material was added nicotinic acid (5.25 mg, 0.043 mmol), HBTU (16.3 mg, 0.043 mmol) and 300 mL of DMF. N-methylmorpholine (9.5 mL, 0.086 mmol) was then added to adjust the pH to 8-9. The reaction mixture was stirred at room temperature and monitored by HPLC until complete. The sample was then diluted with H₂O and purified directly by reversed-phase HPLC (preparative Vydac C18 column (2.5 cm), 0.45%/min gradient of 9 to 27% acetonitrile containing 0.1% trifluoroacetic acid) to afford the title compound as the di-trifluoroacetate salt. (9.72 mg, 32.1%) Mass spec (ESI): 476.2

35

Example 27

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- Benzyl N-(3-chloromethylbenzoyl)-3-aminopropionate (XVIII). This compound was synthesized in a similar way as for I from 3-chloromethylbenzoyl chloride (3 mmol, 426 mL), benzyl 3-aminopropionate toluenesulfonic acid salt (3.2 mmol, 1.12 g) and triethylamine (7 mmol, 0.98 mL). Crystallization from ether-petroleum ether gave 1.0 g (100%) product. NMR (DMSO-d₆): δ 8.62 (t, 1H); 7.88 (s, 1H); 7.78 (d, 1H); 7.46 (t, 1H); 7.32 (m, 5H); 5.10 (s, 2H); 4.80 (s, 2H); 3.52 (m, 2H); 3.65 (t, 2H).
- 10 Benzyl N-(3-(4-cyanophenyloxymethyl)benzoyl)-3-aminopropionate (XIX) A mixture of XVIII (2.5 mmol, 829 mg), 4-cyanophenol (2.5 mmol, 298 mg) and potassium carbonate (5 mmol, 691 mg) in 15 mL DMF was stirred at 80° C for 5 hours and then cooled to room temperature.
- 15 The same work-up as for II and crystallization from ether-petroleum ether gave 1 g (97%) crystalline product. NMR (DMSO-d₆): δ 8.62 (t, 1H); 7.92 (s, 1H); 7.80 (d, 2H); 7.78 (d, 1H); 7.62 (d, 1H); 7.50 (t, 1H); 7.32 (m, 5H); 7.20 (d, 2H); 5.24 (s, 2H); 5.10 (s, 2H);
- 20 3.52 (m, 2H); 2.66 (t, 2H).
- Methyl N-(3-(4-amidinophenyloxymethyl)benzoyl)-3-aminopropionate TFA salt (XX). XIX (2 mmol, 830 mg) was dissolved in 20 mL methanol and HCl gas was bubbled through for 1 hour. The solution was stirred for 1 hour
- 25 and then concentrated. The residue was taken up in 20 mL 2 M ammonia in methanol and the solution was stirred for 5 hours and then concentrated. The residue was taken up in methanol and water. The solution was filtered and purified on reversed phase HPLC to give 650
- 30 mg (69%) product. NMR (DMSO-d₆): δ 9.18 (s, 2H); 8.90 (s, 2H); 8.62 (t, 1H); 7.85 (s, 1H); 7.82 (d, 2H); 7.80 (d, 1H); 7.61 (d, 1H); 7.50 (t, 3H); 7.24 (d, 2H); 5.30 (s, 2H); 3.60 (s, 3H); 3.50 (m, 2H); 2.60 (t, 2H).
- N-(3-(4-amidinophenyloxymethyl)benzoyl)-3-aminopropionic acid TFA salt (XXI). XX (0.21 mmol, 100 mg) was dissolved in 2 mL methanol and 2 mL 1 N NaOH and after 1 hour the solution was acidified with TFA to pH 3.

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Purification on reversed phase HPLC gave 85 mg (88%) product. ESI (M+H)⁺: Calc. 342.2; Found 342.2.

5

Example 53(= Example 1)

Methyl N²-Cbz-L-2,3-diaminopropionate HCl salt (V).

N²-Cbz-L-2,3-diaminopropionic acid (10 mmol, 2.39 g) was dissolved in 20 mL methanol and 20 mL 4 N HCl in dioxane and the solution was stirred for 2 hours and then concentrated to give 2.74 g (95%) solid product. NMR (DMSO-d₆): δ 8.38 (b, 3H); 7.96 (d, 1H); 7.38 (m, 5H); 5.05 (s, 2H); 4.44 (m, 1H); 3.66 (s, 3H); 3.14 (m, 2H).

15 Methyl N²-Cbz-N³-(3-chloromethylbenzoyl)-L-2,3-diaminopropionate (VI). To a solution of 3-chloromethylbenzoyl chloride (5 mmol, 0.71 mL) and V (5.3 mmol, 1.53 g) in 20 mL chloroform cooled in an ice bath was added triethylamine (11 mmol, 1.53 mL). The solution was stirred for 3 hours and then concentrated. The residue was taken up in ethyl acetate and the solution was washed with citric acid, brine, sodium bicarbonate and brine, dried (MgSO₄), and concentrated to give 2.1 g (100%) oily crude product. NMR (DMSO-d₆):
25 δ 8.62 (t, 1H); 7.86 (s, 1H); 7.79 (d, 1H); 7.60 (d, 1H); 7.48 (t, 1H); 7.34 (m, 5H); 5.02 (s, 2H); 4.82 (s, 2H); 4.35 (m, 1H); 3.62 (s, 3H); 3.55 (m, 2H).

Methyl N²-Cbz-N³-(3-(4-cyanophenyloxymethyl)benzoyl)-L-2,3-diaminopropionate (VII). A solution of VI (5 mmol, 2.0 g), 4-cyanophenol (5 mmol, 596 mg) and potassium carbonate (8 mmol, 1.1 g) in 10 mL DMF was heated at 80° C for 16 hours and then cooled to room temperature. Dilute citric acid solution was added followed by ethyl acetate. The organic layer was separated, washed with
35 citric acid, brine, sodium bicarbonate and brine, dried (MgSO₄), and concentrated. Purification on a silica gel column using ethyl acetate/hexane gave 1.35 g (55%) pure

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product. NMR (DMSO- d_6): δ 8.61 (t, 1H); 7.91 (s, 1H); 7.80 (d, 2H); 7.78 (d, 1H); 7.62 (d, 1H); 7.52 (t, 1H); 7.34 (m, 5H); 7.20 (d, 2H); 5.25 (s, 2H); 5.02 (s, 2H); 4.34 (m, 1H); 3.61 (s, 3H); 3.60 (m, 2H).

5 Methyl N²-Cbz-N³-(3-(4-amidinophenyloxymethyl)benzoyl)-L-2,3-diaminopropionate TFA salt (VIII). VII (2 mmol, 975 mg) was dissolved in 20 mL methanol and 20 ml 4 N HCl in dioxane and the solution was stirred for 36 hours and then concentrated. The residue was taken up in 30
10 mL 2 M ammonia in methanol and the solution was stirred for one day. Insoluble material was filtered off and the solution was concentrated. The residue was taken up in DMF and water and the solution was purified by reversed phase HPLC to give 150 mg pure product. NMR
15 (DMSO- d_6): δ 9.15 (s, 2H); 8.92 (s, 2H); 7.9.1 (s, 1H); 7.80 (d, 2H); 7.78 (d, 1H); 7.62 (d, 1H); 7.52 (t, 1H); 7.34 (m, 5H); 7.22 (d, 2H); 5.30 (s, 2H); 5.02 (s, 2H); 4.35 (m, 1H); 3.61 (s, 3H); 3.60 (m, 2H).
N²-Cbz-N³-(3-(4-amidinophenyloxymethyl)benzoyl)-L-2,3-
20 diaminopropionic acid TFA salt (IX). VIII (50 mg) was dissolved in 2 mL methanol and 2 mL 1 N NaOH and after one hour, the solution was acidified with HCl. Purification on reversed phase HPLC gave 30 mg product. ESI (M+H)⁺: Calcd 491.2; Found 491.2.

25

Example 72a1-t-butoxycarbonyl-4-hydroxypiperidine

A solution of 4-hydroxypiperidine (5.05g; 0.05mole) in
30 100ml of tetrahydrofuran was stirred and cooled in an ice-water bath. Di-tert.butylcarbonate (10.9g; 0.05mole) was added and stirring was continued at room temperature for 3hrs. The solvent was removed under reduced pressure. An oily residue was triturated with petroleum
35 ether. Recrystallization from petroleum ether yielded 9.21g (92%). Rf (silica gel) = 0.42 (ethyl acetate/n-hexane 1:9).

Ethyl 3-(N-BOC-piperidinooxymethyl)benzoate

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N-Boc-4-hydroxypiperidine (1.98g; 0.01mole) was dissolved in 10 ml of dimethylformamide and cooled in a 0 ° C ice bath. To this mixture sodium hydride, 60% suspension in an oil (0.6g; 0.015mole) was added and an argon was passed through the reaction flask. The mixture was stirred 60 min. in the ice bath (under an argon atmosphere) before adding ethyl-3-(chloromethyl) benzoate. The reaction mixture was stirred at room temp. for 48hrs and reaction was quenched with 30ml of ethyl alcohol. The solvents were removed under reduced pressure. The residue was dissolved in ethyl acetate and extracted with 5% citric acid, brine and water. An organic fraction was dried over anhydrous magnesium sulfate. This material was further purified by flash chromatography (silica gel) using chloroform to give the title compound (B). $R_f = 0.29$ (Ethyl acetate/n-hexane 2:8) (M+1) = 363

3-(BOC-piperidinooxymethyl)benzoic acid

To a solution of ethyl 3-(Boc-piperidinooxymethyl) benzoate (0.7g; 0.0019mole) in ethanol (40ml), cooled to 0°C in an ice bath was added a solution of sodium hydroxide (24ml; 1N). After 2hrs the reaction mixture was reduced to 1/2 of starting volume, pH adjusted to 3 with HCl and the solvent removed under reduced pressure. The white precipitate (NaCl) formed upon the addition of the ethanol to the dry residue was filtered off. The filtrate was concentrate under reduced pressure to the colorless oil. This material was taken to the next step of synthesis without further purification. Yield : 0.58g (89.2%) $R_f = 0.65$ Chloroform/methanol 9:1

Ethyl N³-[3-(BOC-piperidinooxymethyl)benzoyl]-N²-Cbz-2,3-diaminopropionate

To a solution of 3-(Boc-piperidinooxymethyl)benzoic acid (0.56g; 0.0016mole) and N³Cbz-L-2,3diaminopropionic acid hydrochloride (0.5g; 0.0016mole) in 5ml dimethylforamide was added diisopropyl-ethyl amine (0.81ml; 0.0046mole). The mixture was stirred 10 min. and HBTU [2-(1H-

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benzotriazol-1-yl)-1,1,3,3-tetramethyluroniumhexafluorophosphate] (0.56g; 0.0016mole) was added as a coupling reagent. The reaction was allowed to proceed overnight at room temperature with stirring. The solvent was evaporated under reduced pressure, the residue was dissolved in 100ml ethyl acetate. This solution was extracted with 5% citric acid, sat. NaCO₃ and brine. The organic layer was dried over anhydrous magnesium sulfate, filtered off and the solvent was evaporated under reduced pressure. This material was taken to the next step of synthesis without further purification. Yield: 0.91g (95.7%) R_f = 0.48 Chloroform/methanol 95:5 (M+Na) = 606

Ethyl N³-[3-(piperidinooxymethyl)benzoyl]-N²-Cbz-2,3-diaminopropionate

Ethyl N³-[3-(Boc-piperidinooxymethyl)benzoyl]-L-N²-Cbz-2,3-di-aminopropionate) 0.9g was dissolved in 100ml 25% trifluoroacetic acid/methylene chloride and 10% of an anisole. The reaction at room temp. was allowed to proceed for 30min. The progress of reaction was followed by TLC (silica gel; chloroform/methanol 95:5). The solvent was evaporated under reduced pressure and the residue was triturated with ethyl ether (3X). The new compound gave a positive Ninhydrin test and was taken to the next step of the synthesis.

Ethyl N³-[3-(1-amidinopiperidinooxymethyl)benzoyl]-N²-Cbz-2,3-diaminopropionate, TFA salt

To a solution of ethyl N³-[3-(piperidinooxymethyl)benzoyl]-L-N²-Cbz-2,3-di-aminopropionate (0.06g; 0.0001mole) and dimethylaminopyridine (0.02g; 0.0002mole) in 1ml ethanol/water (3:1) was added formamidine sulfonic acid. The progress of reaction was followed by HPLC (Vydac C-18 analytical from 10% to 70% buffer B; 1% per min. Buffer A: 99.9% water 0.1% TFA Buffer B: 90.9% acetonitrile, 9.9% water, 0.1% TFA). The reaction was allowed to proceed overnight. Purification was accomplished by HPLC on a

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preparative Vydac C-18 column (the same program as above) and than lyophilized to give the TFA salt of the title compound. (M+1) = 526.

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Example 84b

3-(Piperidin-4-yl)propan-1-ol p-toluenesulfonate: To a solution of 3-(4-pyridyl)propan-1-ol (15.13 g, 0.1103 mol) in EtOH (100 mL) was added p-TsOH (20.98 g, 0.1103 mol) and PtO₂ (1.5 g, 6.6 mmol). The resulting mixture was placed on a Parr apparatus and hydrogenated at 55 p.s.i. After 6 hr, the mixture was filtered (EtOH wash) and the filtrate concentrated in vacuo, giving 36.78 g (>100%) of the desired piperidine; ¹H NMR (300 MHz, CDCl₃) δ 7.7 (d, 2H), 7.2 (d, 2H), 3.55 (t, 2H), 3.3 (m, 4H), 2.95 (bt, 2H), 2.38 (s, 3H), 1.95 (bd, 2H), 1.58 (m, 2H), 1.3 (m, 3H).

3-(N-t-Butyloxycarbonylpiperidin-4-yl)propan-1-ol: To a mixture of 3-(piperidin-4-yl)propan-1-ol p-toluenesulfonate (19.0 g, 57 mmol) in 2M NaOH (40 mL, 80 mmol) and t-BuOH (50 mL) was added di-tert-butyl dicarbonate (13.7 g, 62.7 mmol). After stirring for 18 hr, it was concentrated in vacuo and water added. The aqueous was extracted with ether (4x) and the ethereal phase washed with saturated Na₂CO₃, saturated NaCl and dried (MgSO₄). Concentration in vacuo, then under vacuum afforded 11.37 g (82%) of the title compound; ¹H NMR (300 MHz, CDCl₃) δ 4.05 (bs, 2H), 3.63 (b, 2H), 2.7 (bt, 2H), 1.6 (m, 5H), 1.45 (s, 9H), 1.3 (m, 3H), 1.1 (m, 2H).

Methyl 4-[3-(N-t-butyloxycarbonylpiperidin-4-yl)propyl-1-oxylbenzoate: To a solution of 3-(N-t-butyloxycarbonylpiperidin-4-yl)propan-1-ol (6.08 g, 25.0 mmol), methyl 4-hydroxybenzoate (4.11 g, 27.0 mmol) and PPh₃ (9.18 g, 35.0 mmol) in THF (180 mL) at -10 °C was added a solution of DEAD (6.09 g, 35.0 mmol) in THF (30 mL) over 1.25 hr. During the addition, a deep red

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solution resulted, which changed to a golden color upon warming to room temperature overnight (18 hours). At this time the solution was concentrated and redissolved in EtOAc. It was then washed with water, 0.1M HCl, 1M NaOH, sat. NaCl and dried (MgSO₄). Concentration gave a solid (~20 g), which was purified using flash chromatography (5-20% EtOAc/hexanes step gradient), affording 5.46 g (58%) of the desired ether after pumping to constant weight; mp 83.0-83.9 °C.

10 4-[3-(N-t-Butyloxycarbonylpiperidin-4-yl)propyl-1-oxylbenzoic acid: To a solution of methyl 4-[3-(N-t-butyloxycarbonylpiperidin-4-yl)propyl-1-oxyl]benzoate (5.37 g, 14.2 mmol) in THF (70 mL) was added 0.5M LiOH (57 mL, 28.5 mmol) and the resulting mixture heated at

15 reflux overnight (18 hr). After cooling to room temperature, the mixture was acidified to pH 4 using 1M HCl and extracted using ether. The ethereal layer was washed with saturated NaCl, dried (MgSO₄) and concentrated in vacuo followed by pumping under vacuum, giving 5.82 g (89%) of the title compound; CIMS: (M + NH₄)⁺ = 381 (100%).

20 4-[3-(N-t-Butyloxycarbonylpiperidin-4-yl)propyl-1-oxyl-N-3-(ethoxycarbonyl)propylbenzamide: To a solution of 4-[3-(N-t-butyloxycarbonylpiperidin-4-yl)propyl-1-oxyl]benzoic acid (727 mg, 2.00 mmol) in DMF (10 mL) was added Et₃N (0.32 mL, 2.3 mmol) followed by TBTU (706 mg, 2.20 mmol). After 15 min, a mixture of β-alanine ethyl ester hydrochloride (338 mg, 2.70 mmol) and Et₃N (0.38 mL, 2.2 mmol) in DMF (10 mL) was added and the resulting

25 mixture stirred for 18 hr at room temperature. The mixture is then diluted with EtOAc, washed with water (4x), 1M HCl, saturated NaHCO₃, saturated NaCl and dried (MgSO₄). Concentration in vacuo then under vacuum afforded 695 mg (78%) of the desired amide; CIMS: (M + NH₄)⁺ = 480 (100%).

30 4-[3-(N-t-Butyloxycarbonylpiperidin-4-yl)propyl-1-oxyl-N-3-carboxypropylbenzamide: To a solution of 4-[3-(N-t-

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butyloxycarbonylpiperidin-4-yl)propyl-1-oxy]-N-3-(ethoxycarbonyl)propylbenzamide (639 mg, 1.38 mmol) in THF (10 mL) was added 0.5M LiOH (6 mL, 3 mmol) and the resulting mixture heated at reflux for 5 min. It was then cooled to room temperature, and acidified to pH 4 using 0.1M HCl. The aqueous was washed with CHCl₃, and the combined extracts dried (MgSO₄) and concentrated in vacuo. Purification of the oily residue using flash chromatography (5% MeOH-CHCl₃) afforded 252 mg (42%) of the acid as a light yellow oil that solidified upon standing; mp 109.6-110.5 °C.

4-[3-(Piperidin-4-yl)propyl-1-oxy]-N-3-carboxypropylbenzamide, TFA salt: To a solution of 4-[3-(N-t-butyloxycarbonylpiperidin-4-yl)propyl-1-oxy]-N-3-carboxypropylbenzamide (250 mg, 1.38 mmol) in CH₂Cl₂ (5 mL) was added TFA (2 mL, 11.8 mmol) and the resulting solution allowed to stand at room temperature for 60 hr. The solvent was evaporated in vacuo and the residue triturated with ether, then with EtOAc, giving 187 mg (41%) of the title compound as a white powder; mp 172.1-172.9 °C.

Example 85

Benzyl N-(3-chloromethylbenzoyl)-DL-3-aminobutyrate (I). To a solution of 3-chloromethylbenzoyl chloride (10 mmol, 1.42 mL) and benzyl DL-3-aminobutyrate toluenesulfonic acid salt (10.5 mmol, 3.84 g) in 30 mL chloroform cooled in an ice bath was added triethylamine (21 mmol, 2.93 mL) and the solution was stirred for 2 h and then concentrated. The residue was taken up in ethyl acetate and washed with dilute citric acid, brine, sodium bicarbonate and brine, dried (MgSO₄), and concentrated. Crystallization from ether-petroleum ether gave 2.9 g (84%) crystalline product. NMR (DMSO-d₆): δ 8.41 (d, 1H); 7.88 (s, 1H); 7.78 (d, 1H); 7.59

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(d, 1H), 7.48 (t, 1H); 7.32 (m, 5H); 5.06 (s, 2H); 4.80 (s, 2H); 4.42 (m, 1H); 2.62 (m, 2H); 1.20 (d, 3H).

Benzyl N-(3-(4-cyanophenyloxymethyl)benzoyl)-DL-3-aminobutyrate (II). A solution of I (5 mmol, 1.73 g),

5 4-cyanophenol (5 mmol, 596 mg), and potassium carbonate (10 mmol, 1.38 g) in 10 mL DMF was heated at 60° C for 18 hours and then cooled to room temperature. Dilute citric acid solution was added followed by ethyl acetate. The organic phase was separated, washed with
10 dilute citric acid, brine, sodium bicarbonate and brine, dried (MgSO₄), and concentrated to give 2.1 g (98%) solid product. NMR (DMSO-d₆): δ 8.40 (d, 1H); 7.90 (s, 1H); 7.78 (m, 3H); 7.61 (d, 1H); 7.48 (t, 1H); 7.28 (m, 5H); 7.20 (d, 2H); 5.23 (s, 2H); 5.04 (s, 2H); 4.41 (m,
15 1H); 2.62 (m, 2H); 1.20 (d, 3H).

Methyl N-(3-(4-amidinophenyloxymethyl)benzoyl)-DL-3-aminobutyrate, TFA salt (III). II (2 mmol, 857 mg) was

dissolved in 20 mL methanol and 20 mL 4 N HCl in dioxane. The mixture was stirred for 24 hours and then
20 concentrated. The residue was taken up in 20 mL 2 M ammonia in methanol and the solution was stirred overnight and then concentrated. The residue was dissolved in DMF and the solution was filtered, diluted with water and purified on HPLC to give 100 mg product.
25 NMR (DMSO-d₆): δ 9.16 (s, 2H); 8.94 (s, 2H); 8.40 (d, 1H); 7.90 (s, 1H); 7.81 (d, 2H); 7.80 (d, 1H); 7.61 (d, 1H); 7.50 (t, 1H); 7.25 (d, 2H); 5.30 (s, 2H); 4.38 (m, 1H); 3.59 (s, 3H); 2.58 (m, 2H); 1.20 (d, 3H).

N-(3-(4-Amidinophenyloxymethyl)benzoyl)-DL-3-

30 aminobutyric acid TFA salt (IV). III (40 mg) was dissolved in 1 mL methanol and 1 ml 1 N NaOH and after 2 hours, the solution was acidified with HCl to pH 3. Purification on reversed phase HPLC gave 30 mg product. ESI (M+H)⁺: Calcd 356.2; Found 356.2.

35

Example 91

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Methyl 3-(4-cyanobenzyloxy)benzoate (X). A mixture of 4-cyanobenzyl bromide (40 mmol, 7.84 g), methyl 3-hydroxybenzoate (40 mmol, 6.08 g) and potassium carbonate (60 mmol, 8.29 g) in 50 mL DMF was stirred at 5 60° C overnight and the solution was cooled to room temperature. To it was added dilute citric acid followed by ethyl acetate. The organic layer was separated, washed with brine, NaHCO₃ and brine, dried (MgSO₄), and concentrated to give a solid. The solid 10 was washed with ether two times to give 6.2 g (60%) product. NMR (DMSO-d₆): δ 7.88 (d, 2H); 7.66 (d, 2H); 7.58 (m, 2H); 7.46 (t, 1H); 7.32 (dd, 1H); 5.30 (s, 2H); 3.84 (s, 3H).

3-(4-cyanobenzyloxy)benzoic acid (XI). X (21.3 mmol, 5.7 g) was dissolved in 50 mL methanol and 50 mL THF and to it was added 30 mL 1 N NaOH. The solution was stirred for 5 hours and acidified with 1 N HCl to give a solid. The solid was isolated by filtration and washed with water to give 5.4 g (100%) product. NMR (DMSO-d₆): 15 δ 7.88 (d, 2H); 7.68 (d, 2H); 7.58 (m, 2H); 7.43 (t, 1H); 20 δ 7.30 (dd, 1H); 5.32 (s, 2H).

Benzyl N-(3-(4-cyanobenzyloxy)benzoyl)-DL-3-aminobutyrate (XII). To a solution of XI (4 mmol, 1.01 g) and benzyl DL-3-aminobutyrate toluenesulfonic acid 25 salt (4.2 mmol, 1.53 g) in 10 mL DMF were added BOP (4.2 mmol, 1.53 g) and triethylamine (15 mmol, 2.1 mL) and the solution was stirred overnight. Dilute citric acid solution was added followed by ethyl acetate. The organic layer was separated, washed with dilute citric 30 acid, brine, NaHCO₃ and brine, dried (MgSO₄), and concentrated to give 1.6 g (94%) oily product. NMR (DMSO-d₆): δ 8.35 (d, 1H); 7.86 (d, 2H); 7.65 (d, 2H); 7.18-7.45 (m, 9H); 5.26 (s, 2H); 5.08 (s, 2H); 4.40 (m, 1H); 2.64 (m, 2H); 1.18 (d, 3H).

35 Methyl N-(3-(4-amidinobenzyloxy)benzoyl)-DL-3-aminobutyrate TFA salt (XIII). To a solution of XII (2 mmol, 857 mg) in 30 mL methanol was bubbled through with

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HCl gas for 1 hour and the solution was stirred for 20 hours and then concentrated. The residue was taken up in 30 mL methanol and ammonia gas was bubbled through for one hour. The mixture was stirred overnight and then concentrated at room temperature. The solid was washed with ether and dissolved in DMF and water.

Purification on reversed phase HPLC gave 240 mg pure product. NMR (DMSO-d₆): δ 9.30 (s, 2H); 9.02 (s, 2H); 8.31 (d, 1H); 7.82 (d, 2H); 7.68 (d, 2H); 7.18-7.45 (m, 4H); 5.30 (s, 2H); 4.34 (m, 1H); 3.58 (s, 3H); 2.58 (m, 2H); 1.18 (d, 3H).

N-(3-(4-amidinobenzoyloxy)benzoyl)-DL-3-aminobutyric acid TFA salt (XIV). XIII (50 mg) was dissolved in 2 mL methanol and 2 mL 1 N NaOH and after one hour, the solution was acidified with TFA to pH 3. Purification on reversed phase HPLC gave 40 mg product. ESI (M+H)⁺: Calc. 356.2; Found 356.2.

Example 92

20

Methyl DL-3-amino-4,4,4-trifluorobutyrate HCl salt (XV).

DL-3-Amino-4,4,4-trifluorobutyric acid (19.1 mmol, 3 g) was dissolved in 20 mL methanol and 20 mL 4 N HCl in dioxane. The solution stood at room temperature overnight and then concentrated to give 4.2 g (100%) solid product. NMR (DMSO-d₆): δ 9.58 (b, 3H); 4.50 (m, 1H); 3.68 (s, 3H); 3.02 (m, 2H).

Methyl N-(3-(4-cyanobenzoyloxy)benzoyl)-DL-3-amino-4,4,4-trifluorobutyrate (XVI). This compound was synthesized in a similar way as for XII from XI (4 mmol, 1.01 g), XV (4.2 mmol, 872 mg), BOP (4.2 mmol, 1.86 g) and triethylamine (15 mmol, 2.1 mL). Purification on a silica gel column using ethyl acetate/hexane gave 720 mg (44%) product. NMR (DMSO-d₆): δ 8.92 (d, 1H); 7.88 (d, 2H); 7.68 (d, 2H); 7.5 (m, 3H); 7.24 (dd, 1H); 5.28 (s, 2H); 5.18 (m, 1H); 3.61 (s, 1H); 2.95 (d, 2H).

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N-(3-(4-amidinobenzyloxy)benzoyl)-DL-3-amino-4,4,4-trifluorobutyric acid TFA salt (XVII). XVI (1.7 mmol, 700 mg) was dissolved in 20 mL methanol and HCl gas was bubbled through for 1 hour. The solution was stirred overnight and then concentrated. The residue was taken up in 20 mL methanol and ammonia gas was bubbled through for 1 hour. The solution was stirred overnight and then concentrated. The major product from this reaction was isolated and characterized by NMR to be N-(3-(4-amidinobenzyloxy)benzoyl)-DL-3-amino-4,4,4-trifluorobutyramide. The small amount of the desired product was isolated by reversed phase HPLC and then saponified with NaOH in methanol to give the title compound. NMR (DMSO-d₆): δ 9.32 (s, 2H); 9.12 (s, 2H); 8.88 (d, 1H); 7.84 (d, 2H); 7.70 (d, 2H); 7.48 (m, 3H); 7.24 (d, 1H); 5.32 (s, 2H); 5.12 (m, 1H); 2.82 (d, 2H). ESI (M+H)⁺: Calc. 410.2; Found 410.2.

Example 117

20 Methyl N³-(3-(4-amidinophenyloxymethyl)benzoyl)-L-2,3-diaminopropionate di-HCl salt (XXXVI). VII (22.5 mmol, 11 g) was dissolved in 100 mL methanol and HCl gas was bubbled through for 1 hour. The solution was stirred overnight and concentrated to give a solid. The solid was dissolved in 100 mL methanol and ammonia gas was bubbled through at 0° C for 30 min. The solution was stirred for 1 hour and concentrated to give 12 g crude product which was used for the next reaction without purification.

30 N³-(3-(4-amidinophenyloxymethyl)benzoyl)-L-2,3-diaminopropionic acid di-TFA salt (XXXVII). XXXVI (100 mg) was purified on reversed phase HPLC to give 20 mg pure product. The product was treated with 1 mL methanol and 0.5 mL 1 N NaOH for 1 hour and then acidified with acetic acid. Purification on reversed phase HPLC gave 15 mg pure product.

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Example 118

Ethyl N²-Cbz-L-2,3-diaminopropionate HCl salt (XXXXII).

This compound was synthesized from N²-Cbz-L-2,3-

- 5 diaminopropionic acid (10 mmol, 2.4 g) in a similar way as for V. Yield 2.67 g (88%). NMR (DMSO-d₆): δ 8.42 (b, 3H); 7.96 (d, 1H); 7.36 (m, 5H); 5.08 (s, 2H); 4.44 (m, 1H); 4.13 (q, 2H); 3.20 (m, 1H); 3.08 (m, 1H); 1.18 (t, 3H).

- 10 Ethyl N²-Cbz-N³-(3-chloromethylbenzoyl)-L-2,3-diaminopropionate (XXXXIII). This compound was

synthesized in a similar way as for VI from XXXXII (8.8 mmol, 2.67 g), 3-chloromethylbenzoyl chloride (9.8 mmol, 1.39 mL) and triethylamine (12 mmol, 1.67 mL).

- 15 Crystallization from ether-petroleum ether gave 2.26 g (61%) product. NMR (DMSO-d₆): δ 8.61 (t, 1H); 7.87 (s, 1H); 7.77 (m, 2H); 7.60 (d, 1H); 7.48 (t, 1H); 7.34 (m, 5H); 5.04 (s, 2H); 4.81 (s, 2H); 4.32 (m, 1H); 4.05 (q, 2H); 3.61 (m, 2H); 1.12 (t, 3H).

- 20 Ethyl N²-Cbz-N³-(3-(4-cyanophenyloxymethyl)benzoyl)-L-2,3-diaminopropionate (XXXXIV). This compound was synthesized in a similar way as for VII from XXXXIII (5 mmol, 2.09 g), 4-cyanophenol (5 mmol, 596 mg) and potassium carbonate (10 mmol, 1.38 g). Yield 2.4 g (96%). NMR (DMSO-d₆): δ 8.62 (t, 1H); 7.94 (s, 1H); 7.80 (m, 4H); 7.64 (d, 1H); 7.52 (t, 1H); 7.34 (m, 5H); 7.20 (d, 2H); 5.27 (s, 2H); 5.05 (s, 2H); 4.34 (m, 1H); 4.04 (q, 2H); 3.64 (m, 2H); 1.12 (t, 3H).

- 30 Ethyl N³-(3-(4-amidinophenyloxymethyl)benzoyl)-L-2,3-diaminopropionate di-HCl salt (XXXXV). This compound was made in a similar way as for XXXVI by treating XXXXIV (4.6 mmol, 2.3 g) with HCl in ethanol and then with ammonia in ethanol. Yield 2.6 g. The crude product was directly used for the next reaction without
- 35 purification.

Ethyl N²-butyryl-N³-(3-(4-amidinophenyloxymethyl)benzoyl)-L-2,3-diaminopropionate

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TFA salt (XXXXVI). To a solution containing XXXXV (0.57 mmol, 400 mg) and NaHCO₃ (1.5 mmol, 120 mg) in 2 mL water, 2 mL acetonitrile and 1 mL DMF cooled in an ice bath was added butyryl chloride (0.8 mmol, 83 μ L). The solution was stirred for 2 hours, filtered and acidified with TFA. Purification on reversed phase HPLC gave 80 mg pure product. NMR (DMSO-d₆): δ 9.15 (s, 2H); 8.93 (s, 2H); 8.64 (t, 1H); 8.24 (d, 1H); 7.93 (s, 1H); 7.81 (d, 2H); 7.79 (d, 1H); 7.63 (d, 1H); 7.52 (t, 1H); 7.25 (d, 2H); 5.30 (s, 2H); 4.45 (m, 1H); 4.04 (q, 2H); 3.59 (m, 2H); 2.10 (t, 2H); 1.50 (m, 2H); 1.10 (t, 3H); 0.84 (t, 3H).

N²-butyryl-N³-(3-(4-amidinophenyloxymethyl)benzoyl)-L-2,3-diaminopropionic acid TFA salt (XXXXVII). This compound was obtained by treating XXXXVI (50 mg) with 2 mL methanol and 1 mL 1 N NaOH and then purification on reversed phase HPLC. Yield 35 mg.

Example 119a

Methyl-N²-3-pyridylacetoxy-N³-[3-(4-amidinophenyloxymethyl)benzoyl]-L-2,3-diaminopropionate
Methyl-N²-tertbutyloxycarbonyl-N³-[3-(4-amidinophenyloxymethyl)-benzoyl]-L-2,3-diaminopropionate
(18.7 mg, 0.032 mmol) was dissolved in 200 mL of trifluoroacetic acid and stirred at room temperature for 5 minutes. Cold diethyl ether was added to the reaction mixture and a white precipitate formed. The supernatant was removed and the precipitate was washed with diethyl ether and dried. To this material was added 3-pyridylacetic acid hydrochloride (5.6 mg, 0.032 mmol), HBTU (12.1 mg, 0.032 mmol) and 250 mL of DMF. N-methylmorpholine (10.5 μ L, 0.096 mmol) was then added to adjust the pH to 8-9. The reaction mix was stirred at room temperature and monitored by HPLC until complete. The sample was then diluted with H₂O and purified directly by reversed-phase HPLC (preparative Vydac C18 column (2.5 cm), 0.45%/min gradient of 9 to 27%

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acetonitrile containing 0.1% trifluoroacetic acid) to afford the title compound as the di-trifluoroacetate salt (7.9 mg, 34.4%) Mass spec (ESI): 490.1.

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Example 123

N²-n-butyloxycarbonyl-N³-[3-(4-amidinobenzoyloxy)-5-isoxazolecarbonyl]-L-2,3-diaminopropionate TFA salt. The compound of Example 142 (0.26 mmol, 150 mg) was dissolved in 2 mL methanol and 2 mL 1 N NaOH and after 45 min, the solution was acidified with acetic acid. Purification on reversed phase HPLC gave 125 mg (86%) product. ESI (M+H)⁺: Calcd 448.2; Found 448.2.

15

Example 142

Methyl N²-n-butyloxycarbonyl-N³-[3-(4-amidinobenzoyloxy)-5-isoxazolecarbonyl]-L-2,3-diaminopropionate TFA salt
20 A. Methyl N²-Cbz-N³-Boc-L-2,3-diaminopropionate HCl salt
N²-Cbz-L-2,3 diaminopropionic acid (10 mmol, 2.39 g) was dissolved in 20 mL methanol and 20 mL 4 N HCl in dioxane and the solution was stirred for 4 hours and then concentrated to give a solid. The solid was washed with
25 ether several times to give 2.50 g (87%) product. NMR (DMSO-d₆): δ 8.38 (b, 3H); 7.96 (d, 1H); 7.38 (m, 5H); 5.05 (s, 2H); 4.44 (m, 1H); 3.66 (s, 3H); 3.14 (m, 2H).
B. Methyl N²-Cbz-N³-Boc-L-2,3-diaminopropionate To a solution of the compound of Part A (16.3 mmol, 4.7 g)
30 and di-tert-butyl dicarbonate (16.3 mmol, 3.56 g) in 30 mL chloroform cooled in an ice bath was added triethylamine (34 mmol, 4.7 mL) and the solution was stirred in the ice bath for 1 hour and at room temperature for 3 hours and concentrated. The residue
35 was taken up in ethyl acetate and the solution was washed with dilute citric acid, brine, NaHCO₃ and brine, dried (MgSO₄), and concentrated. Crystallization from

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ether/petroleum ether gave 5.2 g (92%) product. NMR (DMSO-d₆): δ 7.60 (d, 1H); 7.35 (m, 5H); 6.88 (t, 1H); 5.02 (s, 2H); 4.14 (m, 1H); 3.60 (s, 3H); 3.28 (m, 2H); 1.37 (s, 9H).

- 5 C. Methyl N³-Boc-L-2,3-diaminopropionate HCO₂H salt A mixture of the compound of Part B (14 mmol, 5.0 g), formic acid (42 mmol, 1.6 mL) and 10 % Pd/C (500 mg) in 40 mL methanol was stirred at room temperature for 1 hour and filtered through a celite. The filtrate was
- 10 concentrated and the residue was triturated with ether-petroleum ether to give 3.7 g (100%) solid product. NMR (DMSO-d₆): δ 8.20 (s, 1H); 6.90 (t, 1H); 5.36 (b, 3H); 3.61 (s, 3H); 3.51 (t, 1H); 3.18 (t, 2H); 1.38 (s, 9H).

- D. Methyl N²-n-butylloxycarbonyl-N³-Boc-L-2,3-
- 15 diaminopropionate To a mixture of the compound of Part C (14 mmol, 3.7 g) and NaHCO₃ (40 mmol, 3.4 g) in 10 mL water and 10 mL THF cooled in an ice bath was added slowly n-butyl chloroformate (16 mmol, 2 mL) over 15 min. After stirring for 1 hour, ethyl acetate was
- 20 added and the solution was washed with dilute citric acid, brine, NaHCO₃ and brine, dried (MgSO₄), and concentrated to give 4.4 g. (100%) oily product. NMR (DMSO-d₆): δ 7.37 (d, 1H); 6.84 (t, 1H); 4.10 (m, 1H); 3.96 (t, 2H); 3.60 (s, 3H); 3.26 (m, 2H); 1.52 (m, 2H);
- 25 1.38 (s, 9H); 1.36 (m, 2H); 0.88 (t, 3H)

- E. Methyl N²-butylloxycarbonyl-L-2,3-diaminopropionate TFA salt The compound of Part D (13.9 mmol, 4.4 g) was dissolved in 25 mL methylene chloride and 35 mL TFA and
- 30 after 1 hour, the solution was concentrated to give an oily product. Yield 4.8 g (100%). NMR (DMSO-d₆): δ 8.02 (b, 3H); 7.68 (d, 2H); 4.38 (m, 1H); 3.99 (t, 2H); 3.68 (s, 3H); 3.22 (m, 1H); 3.06 (m, 1H); 1.55 (m, 2H); δ 1.34 (m, 2H); 0.89 (t, 3H).

- 35 F. Methyl 3-(4-cyanobenzyloxy)-5-isoxazolecarboxylate. A mixture of o-bromo-p-tolunitrile (18.8 mmol, 3.69 g), methyl 3-hydroxy-5-isoxazolecarboxylate (18.8 mmol, 2.69

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g) and potassium carbonate (25 mmol, 3.5 g) was heated at 50° C overnight. After cooling to room temperature, the solution was added to 1% citric acid and the precipitate was filtered, washed with water and cold ether several times and dried. Yield 4.2 g (87%). NMR (DMSO-d₆): δ 7.90 (d, 2H); 7.68 (d, 2H); 7.18 (s, 1H); 5.43 (s, 2H); 3.90 (s, 3H).

G. 3-(4-cyanobenzoyloxy)-5-isoxazolecarboxylic acid. The compound of part F (15 mmol, 3.87 g) was dissolved in 20 mL THF and 30 mL methanol and to it was added 30 mL 1 N NaOH. After stirring at room temperature for 1 hour, the solution was reduced to 50 mL by concentration at 25° C and acidified with 1 N HCl to pH 3. The precipitate was filtered, washed with water several times and dried. Crystallization from ethyl acetate/petroleum ether gave 3.2 g (87%) product. NMR (DMSO-d₆): δ 7.90 (d, 2H); 7.68 (d, 2H); 7.02 (s, 1H); 5.42 (s, 2H).

H. Methyl N²-n-butyloxycarbonyl-N³-3-[4-(cyanobenzoyloxy)-5-carbonyl-L-2,3-diaminopropionate]. To a solution of the compound of part E (14 mmol, 4.8 g) and the compound of part G (14 mmol, 3.2 g) in 30 mL DMF was added triethylamine (45 mmol, 6.3 mL) followed by BOP (14 mmol, 6.2 g) and the solution was stirred at room temperature for 5 hours. Ethyl acetate was added and the solution was washed with dilute citric acid, brine, NaHCO₃ and brine, dried (MgSO₄), and concentrated. The solid was washed with cold ether to give 4.1 g (66%) product. NMR (DMSO-d₆): δ 8.97 (t, 1H); 7.90 (d, 2H); 7.68 (d, 2H); 7.58 (d, 1H); 6.91 (s, 1H); 5.41 (s, 2H); 4.28 (m, 1H); 3.95 (t, 2H); 3.61 (s, 3H); 3.59 (m, 2H); 1.52 (m, 2H); 1.32 (m, 2H); 0.87 (t, 3H).

I. Methyl N²-n-butyloxycarbonyl-N³-[3-(4-amidinobenzoyloxy)-5-isoxazolecarbonyl-L-2,3-diaminopropionate] TFA salt. The compound of Part H (9.2 mmol, 9.2 g) was suspended in 60 mL methanol and to it was bubbled with HCl gas in an ice bath for 1 hour. The solution was stirred at room temperature overnight and

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concentrated. The residue was taken up in 50 mL methanol and ammonium carbonate (25 mmol, 2.4 g) was added. The mixture was stirred overnight and concentrated.

Purification on reversed phase HPLC gave 3.45 g (65%)

5 product. ESI (M+H)⁺: Calcd 462.2; Found 462.3.

Example 479

(A). Methyl 3-(N-Boc-4-piperidinylmethoxy)-5-isoxazolecarboxylate. To a solution of N-Boc-4-piperidinylmethanol (15 mmol, 3.22 g), methyl 3-hydroxy-5-isoxazolecarboxylate (10 mmol, 1.43 g) and triphenyl phosphine (15 mmol, 3.93 g) in 20 mL THF was added diethyl azodicarboxylate (15 mmol, 2.36 g) and the solution was stirred overnight. The solution was reduced to a small amount by concentration and purification on silica gel column using 25% ethyl acetate/petroleum ether gave 1.88 g (40%) product. NMR (DMSO-d₆): δ 7.08 (s, 1H); 4.12 (d, 2H); 3.97 (m, 2H); 3.88 (s, 3H); 2.72 (m, 2H); 1.96 (m, 1H); 1.70 (m, 2H); 1.40 (s, 9H); 1.14 (m, 2H).

B. 3-(N-Boc-4-piperidinylmethoxy)-5-isoxazolecarboxylic acid. The compound of Part A (5.5 mmol, 1.7 g) was dissolved in 10 mL methanol and 7 mL 1 N NaOH and after 1 hour, the solution was acidified with 10 % citric acid and extracted with ether. The ether layer was washed with brine, dried (MgSO₄), and concentrated to give 1.62 (100%) product. NMR (DMSO-d₆): δ 6.94 (s, 1H); 4.10 (d, 2H); 3.97 (m, 2H); 2.72 (m, 2H); 1.96 (m, 1H); 1.70 (m, 2H); 1.39 (s, 9H); 1.14 (m, 2H).

C. Methyl N²-n-butyloxycarbonyl-N³-[3-(N-Boc-4-piperidinylmethoxy)-5-isoxazolecarbonyl]-L-2,3-diaminopropionate. To a solution of the compound of Part B (5.7 mmol, 1.7 g) and the compound of Example 142, Part E (6.84 mmol, 1.74 g) in 10 mL DMF cooled in an ice bath was added diisopropylethylamine (22.8 mmol, 3.97 mL) followed by BOP (6.27 mmol, 2.77 g). The mixture was

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stirred at room temperature overnight. Ethyl acetate was added and the solution was washed with 0.5 N HCl, brine, NaHCO₃ and brine, dried (MgSO₄), and concentrated to give 2.8 g (98%) product. NMR (DMSO-d₆): δ 8.92 (t, 1H);

5 7.56 (d, 1H); 6.81 (s, 1H); 4.27 (m, 1H); 4.10 (cl, 2H); 3.96 (m, 4H); 3.61 (s, 3H); 3.57 (m, 2H); 2.72 (m, 2H); 1.96 (m, 1H); 1.70 (m, 2H); 1.50 (m, 2H); 1.40 (s, 9H); 1.32 (m, 2H); 1.14 (m, 2H); 0.88 (t, 3H).

D. Methyl N²-n-butyloxycarbonyl-N³-[3-(4-piperinylmethoxy)-5-isoxazolecarbonyl]-L-2,3-diaminopropionate TFA salt. The compound of part C (5.6 mmol, 2.8 g) was dissolved in 50 mL 60% TFA/methylene chloride and after 30 min, the solution was concentrated. Ether was added and no precipitation
15 formed. The ether was removed and the residue was dried to give 3.3 g (>100%) product. NMR (DMSO-d₆): δ 8.98 (t, 1H); 8.68 (b, 1H); 8.34 (b, 1H); 7.58 (d, 1H); 6.83 (s, 1H); 4.27 (m, 1H); 4.14 (d, 2H); 3.95 (t, 2H); 3.60 (s, 3H); 3.57 (m, 2H); 3.32 (m, 2H); 2.92 (m, 2H); 2.10 (m,
20 1H); 1.50 (m, 2H); 1.44 (M, 2H); 0.88 (t, 3H).

E. Methyl N²-n-butyloxycarbonyl-N³-[3-(N, N'-diCbzamidino-4-piperidinylmethoxy)-5-isoxazolecarbonyl]-L-2,3-diaminopropionate. A solution of the compound of Part D (2 mmol, 1.02 g), N, N'-diCbz-S-methylisothiurea
25 (1.7 mmol, 585 mg) and 4-dimethylaminopyridine (2 mmol, 244 mg) in 6 mL DMF was stirred at room temperature for 2 days. Ethyl acetate was added and the solution was washed with 0.5 N HCl, brine, NaHCO₃ and brine, dried (MgSO₄), and concentrated. The crude product was
30 purified on a silica gel column using ethyl acetate/hexane (2:3) to give 870 mg (63%) product. NMR (DMSO-d₆): δ 10.08 (s, 1H); 8.92 (t, 1H); 7.57 (d, 1H); 7.35 (m, 10H); 6.82 (s, 1H); 5.08 (b, 2H); 4.94 (b, 2H); 4.26 (m, 1H); 4.12 (d, 2H); 4.08 (m, 2H); 3.95 (t, 2H);
35 3.61 (s, 3H); 3.57 (m, 2H); 2.92 (m, 2H); 2.06 (m, 1H); 1.76 (m, 2H); 1.50 (m, 2H); 1.30 (m, 2H); 1.25 (m, 2H); 0.88 (t, 3H).

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F. Methyl N²-n-butyloxycarbonyl-N-[3-(N-amidino-4-piperidinylmethoxy)-5-isoxazolecarbonyl]-L-2,3-diaminopropionate TFA salt. A mixture of the compound of Part E (1.09 mmol, 800 mg), 10% Pd/C and methanesulfonic acid (2 mmol, 130 μ L) in 5 mL DMF was hydrogenated at atmospheric pressure overnight. The catalyst was filtered off and the solution was diluted with water. Purification on reversed phase HPLC gave 325 mg (50%) product. NMR (DMSO-d₆): δ 8.96 (t, 1H); 7.58 (d, 1H); 7.34 (s, 1H); 6.84 (s, 1H); 4.27 (m, 1H); 4.13 (d, 2H); 3.95 (t, 2H); 3.88 (m, 2H); 3.61 (s, 3H); 3.57 (m, 2H); 3.04 (m, 2H); 2.10 (m, 1H); 1.80 (m, 2H); 1.50 (m, 2H); 1.32 (m, 2H); 1.26 (m, 2H); 0.88 (t, 3H).

Utility

The compounds of this invention possess antiplatelet efficacy, as evidenced by their activity in standard platelet aggregation assays or platelet fibrinogen binding assays, as described below. A compound is considered to be active in these assays if it has an IC₅₀ value of less than about 1 mM. Platelet aggregation and fibrinogen binding assays which may be used to demonstrate the antiplatelet activity of the compounds of the invention are described below.

Platelet Aggregation Assay: Venous blood was obtained from the arm of a healthy human donor who was drug-free and aspirin-free for at least two weeks prior to blood collection. Blood was collected into 10 mL citrated Vacutainer tubes. The blood was centrifuged for 15 minutes at 150 x g at room temperature, and platelet-rich plasma (PRP) was removed. The remaining blood was centrifuged for 15 minutes at 1500 x g at room temperature, and platelet-poor plasma (PPP) was removed. Samples were assayed on a aggregometer (PAP-4 Platelet

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Aggregation Profiler), using PPP as the blank (100% transmittance). 200 μ L of PRP was added to each micro test tube, and transmittance was set to 0%. 20 μ L of various agonists (ADP, collagen, arachidonate, epinephrine, thrombin) were added to each tube, and the aggregation profiles were plotted (% transmittance versus time). The results are expressed as % inhibition of agonist-induced platelet aggregation. For the IC₅₀ evaluation, the test compounds were added at various concentrations prior to the activation of the platelets.

Purified GPIIb/IIIa-Fibrinogen Binding ELISA

The following reagents are used in the GPIIb/IIIa-fibrinogen binding ELISA:

- purified GPIIb/IIIa (148.8 μ g/mL);
- biotinylated fibrinogen (~ 1 mg/mL or 3000 nM);
- anti-biotin alkaline phosphatase conjugate (Sigma no. A7418);
- flat-bottom, high binding, 96-well plates (Costar Cat. no. 3590);
- phosphatase substrate (Sigma 104) (40 mg capsules);
- bovine serum albumin (BSA) (Sigma no. A3294);
- Alkaline Phosphatase buffer - 0.1 M glycine-HCl, 1 mM MgCl₂.6H₂O, 1 mM ZnCl₂, pH 10.4;
- Binding buffer - 20 mM Tris-HCl, 150 mM NaCl, 1 mM CaCl₂.2H₂O, 0.02% NaN₃, pH 7.0;
- Buffer A - 50 mM Tris-HCl, 100 mM NaCl, 2 mM CaCl₂.2H₂O, 0.02% NaN₃, pH 7.4;
- Buffer A + 3.5% BSA (Blocking buffer);
- Buffer A + 0.1% BSA (Dilution buffer);
- 2N NaOH.

The following method steps are used in the GPIIb/IIIa-fibrinogen binding ELISA:

- Coat plates with GPIIb/IIIa in Binding buffer (125 ng/100 μ L/well) overnight at 4 °C (Leave first column

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uncoated for non-specific binding). Cover and freeze plates at -70 °C until used. Thaw plate 1 hour at room temperature or overnight at 4 °C. Discard coating solution and wash once with 200 uL Binding buffer per well. Block plate 2 hours at room temperature on shaker with 200 ul Buffer A + 3.5% BSA (Blocking buffer) per well. Discard Blocking buffer and wash once with 200 uL Buffer A + 0.1% BSA (Dilution buffer) per well. Pipet 11 uL of test compound (10X the concentration to be tested in Dilution buffer) into duplicate wells. Pipet 11 ul Dilution buffer into non-specific and total binding wells. Add 100 uL Biotinylated fibrinogen (1/133 in Dilution buffer, final concentration = 20 nM) to each well. Incubate plates for 3 hours at room temperature on a plate shaker. Discard assay solution and wash twice with 300 uL Binding buffer per well. Add 100 uL Anti-biotin alkaline phosphatase conjugate (1/1500 in Dilution buffer) to each well. Incubate plates for 1 hour at room temperature on plate shaker. Discard conjugate and wash twice with 300 5l Binding buffer per well. Add 100 uL Phosphatase substrate (1.5 mg/ml in Alkaline phosphatase buffer) to each well. Incubate plate at room temperature on shaker until color develops. Stop color development by adding 25 uL 2N NaOH per well. Read plate at 405 nm. Blank against non-specific binding (NSB) well. % Inhibition is calculated as $100 - (\text{Test Compound Abs} / \text{Total Abs}) \times 100$.

Platelet-Fibrinogen Binding Assay: Binding of ^{125}I -fibrinogen to platelets was performed as described by Bennett et al. (1983) Proc. Natl. Acad. Sci. USA 80: 2417-2422, with some modifications as described below. Human PRP (h-PRP) was applied to a Sepharose column for the purification of platelet fractions. Aliquots of platelets (5×10^8 cells) along with 1 mM calcium chloride were added to removable 96 well plates prior to the activation of the human gel purified platelets

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(h-GPP). Activation of the human gel purified platelets was achieved using ADP, collagen, arachidonate, epinephrine, and/or thrombin in the presence of the ligand, ^{125}I -fibrinogen. The ^{125}I -fibrinogen bound to the activated platelets was separated from the free form by centrifugation and then counted on a gamma counter. For an IC_{50} evaluation, the test compounds were added at various concentrations prior to the activation of the platelets.

10

The compounds of Formula I of the present invention may also possess thrombolytic efficacy, that is, they are capable of lysing (breaking up) already formed platelet-rich fibrin blood clots, and thus are useful in treating a thrombus formation, as evidenced by their activity in the tests described below. Preferred compounds of the present invention for use in thrombolysis include those compounds having an IC_{50} value (that is, the molar concentration of the compound capable of achieving 50% clot lysis) of less than about 1 mM, more preferably an IC_{50} value of less than about 0.1 mM.

Thrombolytic Assay: Venous blood was obtained from the arm of a healthy human donor who was drug-free and aspirin free for at least two weeks prior to blood collection, and placed into 10 ml citrated Vacutainer tubes. The blood was centrifuged for 15 minutes at 1500 x g at room temperature, and platelet rich plasma (PRP) was removed. To the PRP was then added 1×10^{-3} M of the agonist ADP, epinephrine, collagen, arachidonate, serotonin or thrombin, or a mixture thereof, and the PRP incubated for 30 minutes. The PRP was centrifuged for 12 minutes at 2500 x g at room temperature. The supernatant was then poured off, and the platelets remaining in the test tube were resuspended in platelet poor plasma (PPP), which served as a plasminogen source.

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The suspension was then assayed on a Coulter Counter (Coulter Electronics, Inc., Hialeah, FL), to determine the platelet count at the zero time point. After obtaining the zero time point, test compounds were added at various concentrations. Test samples were taken at various time points and the platelets were counted using the Coulter Counter. To determine the percent of lysis, the platelet count at a time point subsequent to the addition of the test compound was subtracted from the platelet count at the zero time point, and the resulting number divided by the platelet count at the zero time point. Multiplying this result by 100 yielded the percentage of clot lysis achieved by the test compound. For the IC₅₀ evaluation, the test compounds were added at various concentrations, and the percentage of lysis caused by the test compounds was calculated.

The compounds of Formula I of the present invention are also useful for administration in combination with anti-coagulant agents such as warfarin or heparin, or antiplatelet agents such as aspirin, piroxicam or ticlopidine, or thrombin inhibitors such as boro peptides, hirudin or argatroban, or thrombolytic agents such as tissue plasminogen activator, anistreplase, urokinase or streptokinase, or combinations thereof.

Table A below sets forth the biological activity of representative compounds of the present invention.

Table A

<u>Example</u> <u>Number</u>	<u>IC₅₀</u>
85	+++
53	+++
110	++

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91	+++
92	+
27	+++
16	+++
16a	++
6a	+++
3a	+++
14	+++
18a	+++
19a	+++
20a	+++
84a	+++
84b	+++
119a	+++
123	+++
142	+++
479	+++
480	++
481	++
482	+
500a	+++
501a	+++

In Table A the biological activity of the compounds is indicated as the IC₅₀ value in the platelet aggregation assay described above. The IC₅₀ values are expressed as: +++ = IC₅₀ of <10 μ M; ++ = IC₅₀ value of 10 μ M to 50 μ M; + = IC₅₀ of 51-100 μ M. As used herein "uM" means micromolar.

10

Dosage and Formulation

The compounds of the present invention can be administered in such oral dosage forms as tablets, capsules (each of which includes sustained release or timed release formulations), pills, powders, granules,

15

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elixirs, tinctures, suspensions, syrups, and emulsions. Likewise, they may also be administered in intravenous (bolus or infusion), intraperitoneal, subcutaneous, or intramuscular form, all using dosage forms well known to those of ordinary skill in the pharmaceutical arts. An effective but non-toxic amount of the compound desired can be employed as an anti-aggregation agent.

The compounds of this invention can be administered by any means that produces contact of the active agent with the agent's site of action, glycoprotein IIb/IIIa (GPIIb/IIIa), in the body of a mammal. They can be administered by any conventional means available for use in conjunction with pharmaceuticals, either as individual therapeutic agents or in a combination of therapeutic agents, such as a second antiplatelet agent such as aspirin or ticlopidine which are agonist-specific. They can be administered alone, but generally administered with a pharmaceutical carrier selected on the basis of the chosen route of administration and standard pharmaceutical practice.

The dosage regimen for the compounds of the present invention will, of course, vary depending upon known factors, such as the pharmacodynamic characteristics of the particular agent and its mode and route of administration; the species, age, sex, health, medical condition, and weight of the recipient; the nature and extent of the symptoms; the kind of concurrent treatment; the frequency of treatment; the route of administration, the renal and hepatic function of the patient, and the effect desired. An ordinarily skilled physician or veterinarian can readily determine and prescribe the effective amount of the drug required to prevent, counter, or arrest the progress of the condition.

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By way of general guidance, the daily oral dosage of each active ingredient, when used for the indicated effects, will range between about 0.001 to 1000 mg/kg of body weight, preferably between about 0.01 to 100 mg/kg of body weight per day, and most preferably between about 1.0 to 20 mg/kg/day. Intravenously, the most preferred doses will range from about 1 to about 10 mg/kg/minute during a constant rate infusion. Advantageously, compounds of the present invention may be administered in a single daily dose, or the total daily dosage may be administered in divided doses of two, three, or four times daily.

The compounds for the present invention can be administered in intranasal form via topical use of suitable intranasal vehicles, or via transdermal routes, using those forms of transdermal skin patches well known to those of ordinary skill in that art. To be administered in the form of a transdermal delivery system, the dosage administration will, of course, be continuous rather than intermittent throughout the dosage regimen.

In the methods of the present invention, the compounds herein described in detail can form the active ingredient, and are typically administered in admixture with suitable pharmaceutical diluents, excipients, or carriers (collectively referred to herein as carrier materials) suitably selected with respect to the intended form of administration, that is, oral tablets, capsules, elixirs, syrups and the like, and consistent with conventional pharmaceutical practices.

For instance, for oral administration in the form of a tablet or capsule, the active drug component can be combined with an oral, non-toxic, pharmaceutically acceptable, inert carrier such as lactose, starch, sucrose, glucose, methyl cellulose, magnesium stearate, dicalcium phosphate, calcium sulfate, mannitol, sorbitol

and the like; for oral administration in liquid form, the oral drug components can be combined with any oral, non-toxic, pharmaceutically acceptable inert carrier such as ethanol, glycerol, water, and the like.

5 Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents, and coloring agents can also be incorporated into the mixture. Suitable binders include starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and
10 synthetic gums such as acacia, tragacanth, or sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes, and the like. Lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium
15 chloride, and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum, and the like.

The compounds of the present invention can also be administered in the form of liposome delivery systems,
20 such as small unilamellar vesicles, large unilamellar vesicles, and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine, or phosphatidylcholines.

Compounds of the present invention may also be
25 coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxypropylmethacrylamide-phenol, polyhydroxyethylaspartamidephenol, or polyethyleneoxide-
30 polylysine substituted with palmitoyl residues. Furthermore, the compounds of the present invention may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polyglycolic acid, copolymers of
35 polylactic and polyglycolic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates, and

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crosslinked or amphoteric block copolymers of hydrogels.

Dosage forms (pharmaceutical compositions) suitable for administration may contain from about 1 milligram to about 100 milligrams of active ingredient per dosage unit. In these pharmaceutical compositions the active ingredient will ordinarily be present in an amount of about 0.5-95% by weight based on the total weight of the composition.

The active ingredient can be administered orally in solid dosage forms, such as capsules, tablets, and powders, or in liquid dosage forms, such as elixirs, syrups, and suspensions. It can also be administered parenterally, in sterile liquid dosage forms.

Gelatin capsules may contain the active ingredient and powdered carriers, such as lactose, starch, cellulose derivatives, magnesium stearate, stearic acid, and the like. Similar diluents can be used to make compressed tablets. Both tablets and capsules can be manufactured as sustained release products to provide for continuous release of medication over a period of hours. Compressed tablets can be sugar coated or film coated to mask any unpleasant taste and protect the tablet from the atmosphere, or enteric coated for selective disintegration in the gastrointestinal tract.

Liquid dosage forms for oral administration can contain coloring and flavoring to increase patient acceptance.

In general, water, a suitable oil, saline, aqueous dextrose (glucose), and related sugar solutions and glycols such as propylene glycol or polyethylene glycols are suitable carriers for parenteral solutions. Solutions for parenteral administration preferably contain a water soluble salt of the active ingredient, suitable stabilizing agents, and if necessary, buffer substances. Antioxidizing agents such as sodium

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bisulfite, sodium sulfite, or ascorbic acid, either alone or combined, are suitable stabilizing agents. Also used are citric acid and its salts and sodium EDTA. In addition, parenteral solutions can contain

5 preservatives, such as benzalkonium chloride, methyl- or propyl-paraben, and chlorobutanol.

Suitable pharmaceutical carriers are described in Remington's Pharmaceutical Sciences, Mack Publishing Company, a standard reference text in this field.

10 Useful pharmaceutical dosage-forms for administration of the compounds of this invention can be illustrated as follows:

Capsules

15 A large number of unit capsules are prepared by filling standard two-piece hard gelatin capsules each with 100 milligrams of powdered active ingredient, 150 milligrams of lactose, 50 milligrams of cellulose, and 6 milligrams magnesium stearate.

20

Soft Gelatin Capsules

A mixture of active ingredient in a digestable oil such as soybean oil, cottonseed oil or olive oil is prepared and injected by means of a positive
25 displacement pump into gelatin to form soft gelatin capsules containing 100 milligrams of the active ingredient. The capsules are washed and dried.

Tablets

30 A large number of tablets are prepared by conventional procedures so that the dosage unit was 100 milligrams of active ingredient, 0.2 milligrams of colloidal silicon dioxide, 5 milligrams of magnesium stearate, 275 milligrams of microcrystalline cellulose,
35 11 milligrams of starch and 98.8 milligrams of lactose. Appropriate coatings may be applied to increase palatability or delay absorption.

Injectable

A parenteral composition suitable for administration by injection is prepared by stirring 1.5% by weight of active ingredient in 10% by volume propylene glycol and water. The solution is made isotonic with sodium chloride and sterilized.

Suspension:

An aqueous suspension is prepared for oral administration so that each 5 mL contain 100 mg of finely divided active ingredient, 200 mg of sodium carboxymethyl cellulose, 5 mg of sodium benzoate, 1.0 g of sorbitol solution, U.S.P., and 0.025 mL of vanillin.

The compounds of the present invention may be administered in combination with a second therapeutic agent selected from: an anti-coagulant agent such as warfarin or heparin; an anti-platelet agent such as aspirin, piroxicam or ticlopidine; a thrombin inhibitor such as a boro-peptide thrombin inhibitor, or hirudin; or a thrombolytic agent such as plasminogen activators, such as tissue plasminogen activator, anistreplase, urokinase or streptokinase. The compound of Formula I and such second therapeutic agent can be administered separately or as a physical combination in a single dosage unit, in any dosage form and by various routes of administration, as described above.

The compound of Formula I may be formulated together with the second therapeutic agent in a single dosage unit (that is, combined together in one capsule, tablet, powder, or liquid, etc.). When the compound of Formula I and the second therapeutic agent are not formulated together in a single dosage unit, the compound of Formula I and the second therapeutic agent (anti-coagulant agent, anti-platelet agent, thrombin inhibitor, and/or thrombolytic agent) may be

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administered essentially at the same time, or in any order; for example the compound of Formula I may be administered first, followed by administration of the second agent (anti-coagulant agent, anti-platelet agent, thrombin inhibitor, and/or thrombolytic agent). When not administered at the same time, preferably the administration of the compound of Formula and the second therapeutic agent occurs less than about one hour apart, more preferably less than about 5 to 30 minutes apart.

10

Preferably the route of administration of the compound of Formula I is oral. Although it is preferable that the compound of Formula I and the second therapeutic agent (anti-coagulant agent, anti-platelet agent, thrombin inhibitor, and/or thrombolytic agent) are both administered by the same route (that is, for example, both orally), if desired, they may each be administered by different routes and in different dosage forms (that is, for example, one component of the combination product may be administered orally, and another component may be administered intravenously).

The dosage of the compound of Formula I when administered alone or in combination with a second therapeutic agent may vary depending upon various factors such as the pharmacodynamic characteristics of the particular agent and its mode and route of administration, the age, health and weight of the recipient, the nature and extent of the symptoms, the kind of concurrent treatment, the frequency of treatment, and the effect desired, as described above.

Although the proper dosage of the compound of Formula I when administered in combination with the second therapeutic agent will be readily ascertainable by a medical practitioner skilled in the art, once armed with the present disclosure, by way of general guidance, where the compounds of this invention are combined with anti-coagulant agents, for example, a daily dosage may

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be about 0.1 to 100 milligrams of the compound of Formula I and about 1 to 7.5 milligrams of the anti-coagulant, per kilogram of patient body weight. For a tablet dosage form, the novel compounds of this invention generally may be present in an amount of about 5 to 10 milligrams per dosage unit, and the anti-coagulant in an amount of about 1 to 5 milligrams per dosage unit.

Where the compounds of Formula I are administered in combination with a second anti-platelet agent, by way of general guidance, typically a daily dosage may be about 0.01 to 25 milligrams of the compound of Formula I and about 50 to 150 milligrams of the additional anti-platelet agent, preferably about 0.1 to 1 milligrams of the compound of Formula I and about 1 to 3 milligrams of antiplatelet agents, per kilogram of patient body weight.

Further, by way of general guidance, where the compounds of Formula I are administered in combination with thrombolytic agent, typically a daily dosage may be about 0.1 to 1 milligrams of the compound of Formula I, per kilogram of patient body weight and, in the case of the thrombolytic agents, the usual dosage of the thrombolytic agent when administered alone may be reduced by about 70-80% when administered with a compound of Formula I.

Where two or more of the foregoing second therapeutic agents are administered with the compound of Formula I, generally the amount of each component in a typical daily dosage and typical dosage form may be reduced relative to the usual dosage of the agent when administered alone, in view of the additive or synergistic effect of the therapeutic agents when administered in combination.

Particularly when provided as a single dosage unit, the potential exists for a chemical interaction between

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the combined active ingredients. For this reason, when the compound of Formula I and a second therapeutic agent are combined in a single dosage unit they are formulated such that although the active ingredients are combined in a single dosage unit, the physical contact between the active ingredients is minimized (that is, reduced). For example, one active ingredient may be enteric coated. By enteric coating one of the active ingredients, it is possible not only to minimize the contact between the combined active ingredients, but also, it is possible to control the release of one of these components in the gastrointestinal tract such that one of these components is not released in the stomach but rather is released in the intestines. One of the active ingredients may also be coated with a sustained-release material which effects a sustained-release throughout the gastrointestinal tract and also serves to minimize physical contact between the combined active ingredients. Furthermore, the sustained-released component can be additionally enteric coated such that the release of this component occurs only in the intestine. Still another approach would involve the formulation of a combination product in which the one component is coated with a sustained and/or enteric release polymer, and the other component is also coated with a polymer such as a lowviscosity grade of hydroxypropyl methylcellulose (HPMC) or other appropriate materials as known in the art, in order to further separate the active components. The polymer coating serves to form an additional barrier to interaction with the other component.

These as well as other ways of minimizing contact between the components of combination products of the present invention, whether administered in a single dosage form or administered in separate forms but at the same time by the same manner, will be readily

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apparent to those skilled in the art, once armed with the present disclosure.

The present invention also includes pharmaceutical kits useful, for example, in the inhibition of platelet aggregation, the treatment of blood clots, and/or the treatment of thromboembolic disorders, which comprise one or more containers containing a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula I. Such kits may further include, if desired, one or more of various conventional pharmaceutical kit components, such as, for example, containers with one or more pharmaceutically acceptable carriers, additional containers, etc., as will be readily apparent to those skilled in the art. Instructions, either as inserts or as labels, indicating quantities of the components to be administered, guidelines for administration, and/or guidelines for mixing the components, may also be included in the kit.

In the present disclosure it should be understood that the specified materials and conditions are important in practicing the invention but that unspecified materials and conditions are not excluded so long as they do not prevent the benefits of the invention from being realized.

The Tables below provide representative compounds of Formula I of the present invention. Also specifically disclosed by the present invention are those compounds listed in the Tables below wherein R¹⁶ is selected from:

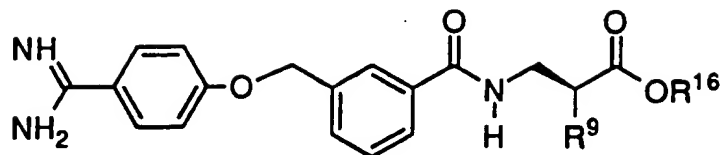
C₁ to C₁₀ alkyl;
methylcarbonyloxymethyl-;
ethylcarbonyloxymethyl-;
t-butylcarbonyloxymethyl-;
cyclohexylcarbonyloxymethyl-;
1-(methylcarbonyloxy)ethyl-;

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- 1- (ethylcarbonyloxy) ethyl-;
1- (t-butylcarbonyloxy) ethyl-;
1- (cyclohexylcarbonyloxy) ethyl-;
i-propyloxy carbonyloxymethyl-;
5 cyclohexylcarbonyloxymethyl-;
t-butyloxy carbonyloxymethyl-;
1- (i-propyloxy carbonyloxy) ethyl-;
1- (cyclohexyloxy carbonyloxy) ethyl-;
1- (t-butyloxy carbonyloxy) ethyl-;
10 dimethylaminoethyl-;
diethylaminoethyl-;
(1,3-dioxa-5-methyl-cyclopenten-2-one-4-
yl)methyl-;
(5-(t-butyl)-1,3-dioxa-cyclopenten-2-one-4-
15 yl)methyl-;
(1,3-dioxa-5-phenyl-cyclopenten-2-one-4-
yl)methyl-;
1- (2- (2-methoxypropyl) carbonyloxy) ethyl-.

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Table 1



<u>Example Number</u>	<u>R⁹</u>	<u>R¹⁶</u>	<u>FAB MS (M+H)⁺</u>
1	NHC (=O) OCH ₂ (C ₆ H ₅)	H	491.2
2	NHC (=O) OC (CH ₃) ₃	H	471
3	NHC (=O) O (CH ₂) ₃ CH ₃	H	
4	NHC (=O) OCH ₂ CH ₃	H	
5	NHC (=O) OCH ₃	H	
6	NHC (=O) CH ₂ CH ₂ (C ₆ H ₅)	H	
7	NHC (=O) CH ₂ C (CH ₃) ₃	H	
8	NHC (=O) (CH ₂) ₄ CH ₃	H	
9	NHC (=O) (CH ₂) ₃ CH ₃	H	455
10	NHC (=O) CH ₂ CH ₃	H	
11	NHC (=O) -CH ₃	H	
12	NHS (=O) ₂ CH ₃	H	
13	NHS (=O) ₂ CH ₂ CH ₃	H	
14	NHS (=O) ₂ (CH ₂) ₃ CH ₃	H	477.2
15	NHS (=O) ₂ (C ₆ H ₅)	H	
16	NHS (=O) ₂ -4- (methyl) phenyl	H	511.2
17	NHS (=O) ₂ CH ₂ (C ₆ H ₅)	H	
18	NHC (=O) -2-pyridyl	H	
19	NHC (=O) -3-pyridyl	H	476
20	NHC (=O) -4-pyridyl	H	

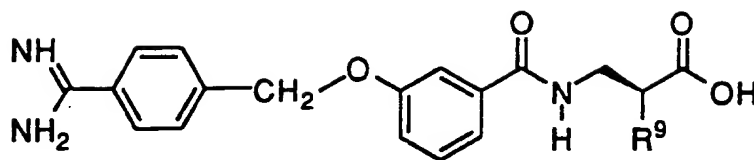
-136-

<u>Example Number</u>	<u>R⁹</u>		<u>FAB MS (M+H)⁺</u>
21	CH ₃	H	
22	CH ₂ CH ₃	H	
23	C ₆ H ₅	H	
24	2-pyridyl	H	
25	3-pyridyl	H	
26	4-pyridyl	H	
27	H	H	342.2
117	NH ₂	H	
118	NHC(=O)O(CH ₂) ₂ CH ₃		
1a	NHC(=O)OCH ₂ (C ₆ H ₅)	CH ₃	
2a	NHC(=O)OC(CH ₃) ₃	CH ₃	471
3a	NHC(=O)O(CH ₂) ₃ CH ₃	CH ₃	471
4a	NHC(=O)OCH ₂ CH ₃	CH ₃	
5a	NHC(=O)OCH ₃	CH ₃	
6a	NHC(=O)CH ₂ CH ₂ (C ₆ H ₅)	CH ₃	503
7a	NHC(=O)CH ₂ C(CH ₃) ₃	CH ₃	
8a	NHC(=O)(CH ₂) ₄ CH ₃	CH ₃	
9a	NHC(=O)(CH ₂) ₃ CH ₃	CH ₃	
10a	NHC(=O)CH ₂ CH ₃	CH ₃	
11a	NHC(=O)-CH ₃	CH ₃	
12a	NHS(=O) ₂ CH ₃	CH ₃	
13a	NHS(=O) ₂ CH ₂ CH ₃	CH ₃	

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<u>Example Number</u>	<u>R⁹</u>	<u>R¹⁶</u>	<u>FAB MS (M+H)⁺</u>
14a	NHS (=O) ₂ (CH ₂) ₃ CH ₃	CH ₃	
15a	NHS (=O) ₂ (C ₆ H ₅)	CH ₃	
16a	NHS (=O) ₂ -4-(methyl)phenyl	CH ₃	511.2
18a	NHC (=O)-2-pyridyl	CH ₃	476.2
19a	NHC (=O)-3-pyridyl	CH ₃	476
20a	NHC (=O)-4-pyridyl	CH ₃	476.1
21a	CH ₃	CH ₃	
22a	CH ₂ CH ₃	CH ₃	
23a	C ₆ H ₅	CH ₃	
24a	2-pyridyl	CH ₃	
25a	3-pyridyl	CH ₃	
26a	4-pyridyl	CH ₃	
27a	H	CH ₃	
117a	NH ₂	CH ₃	
118a	NHC (=O) O (CH ₂) ₂ CH ₃	CH ₃	
119a	NHC (=O) CH ₂ (3-pyridyl)	CH ₃	490
500a	NHC (=O) CH ₂ (2-pyridyl)	CH ₃	490.2
501a	NHC (=O) CH ₂ (4-pyridyl)	CH ₃	490.3
3b	NHC (=O) (CH ₂) ₃ CH ₃	C ₂ H ₅	455

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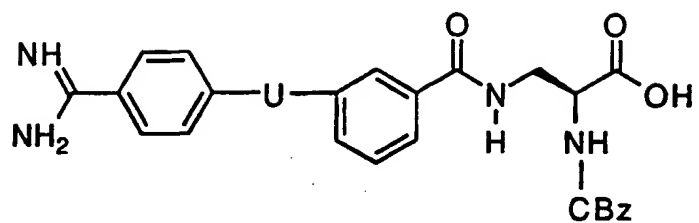
Table 2

<u>Example Number</u>	<u>R⁹</u>	<u>FAB MS (M+H)⁺</u>
28	NHC (=O) OCH ₂ (C ₆ H ₅)	
29	NHC (=O) OC (CH ₃) ₃	
30	NHC (=O) O (CH ₂) ₃ CH ₃	
31	NHC (=O) OCH ₂ CH ₃	
32	NHC (=O) OCH ₃	
33	NHC (=O) CH ₂ CH ₂ (C ₆ H ₅)	
34	NHC (=O) CH ₂ C (CH ₃) ₃	
35	NHC (=O) (CH ₂) ₄ CH ₃	
36	NHC (=O) (CH ₂) ₃ CH ₃	
37	NHC (=O) CH ₂ CH ₃	
38	NHC (=O) -CH ₃	
39	NHS (=O) ₂ CH ₃	
40	NHS (=O) ₂ CH ₂ CH ₃	
41	NHS (=O) ₂ (CH ₂) ₃ CH ₃	
42	NHS (=O) ₂ (C ₆ H ₅)	
43	NHS (=O) ₂ CH ₂ (C ₆ H ₅)	
44	NHC (=O) -2-pyridyl	
45	NHC (=O) -3-pyridyl	
46	NHC (=O) -4-pyridyl	

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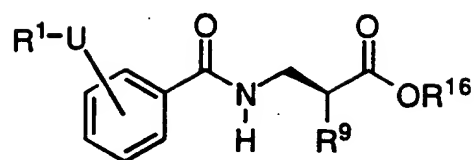
<u>Example Number</u>	<u>R⁹</u>	<u>FAB MS (M+H)⁺</u>
47	CH ₃	
48	CH ₂ CH ₃	
49	C ₆ H ₅	
50	2-pyridyl	
51	3-pyridyl	
52	4-pyridyl	

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Table 3

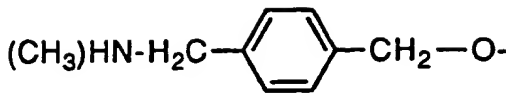
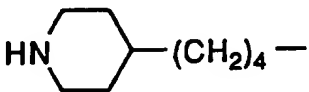
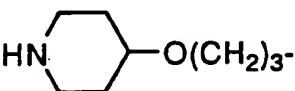
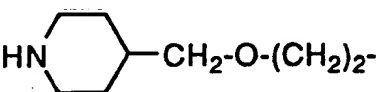
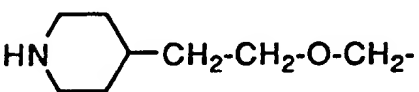
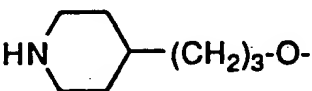
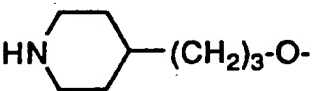
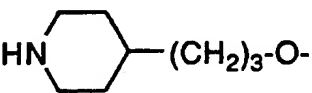
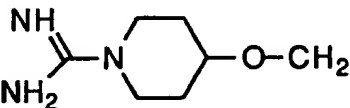
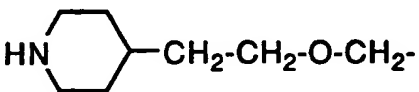
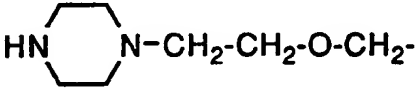
<u>Example Number</u>	<u>U</u>	<u>FAB MS (M+H)⁺</u>
53	OCH ₂	491.2
54	CH ₂ O	
55	SCH ₂	
56	CH ₂ S	
57	NHCH ₂	
58	CH ₂ NH	
59	N(CH ₃)CH ₂	
60	CH ₂ N(CH ₃)	
61	S(=O)CH ₂	
62	CH ₂ S(=O)	
63	S(=O) ₂ CH ₂	
64	CH ₂ S(=O) ₂	
65	S(=O) ₂ NH	
66	NHS(=O) ₂	
67	CH ₂ CH ₂	
68	CH=CH	
69	C≡C	

Table 4



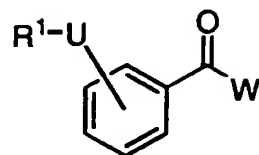
Ex. No.	R ¹ -U	R ⁹	R ¹⁶	FAB MS (M+H) +
70		NHCbz	H	
71	3-	NHCbz	H	
72	3-	NHCbz	H	
73	3-	NHCbz	H	
74	3-	NHCbz	H	
75	3-	NHCbz	H	
76	3-	NHCbz	H	
77	3-	NHCbz	H	
78	3-	NHCbz	H	

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Ex. No.	R ¹ -U	H	FAB MS (M+H) +
79	3- 	NHCbz H	
80	3- 	NHCbz H	
81	3- 	NHCbz H	
82	3- 	NHCbz H	
83	3- 	NHCbz H	
84	3- 	NHCbz H	
84a	3- 	H H	335
84b	3- 	H H	335
72a	4- 	NHCbz CH ₃	526
83a		NHCbz CH ₃	498
120b		NHCbz C ₂ H ₅	513

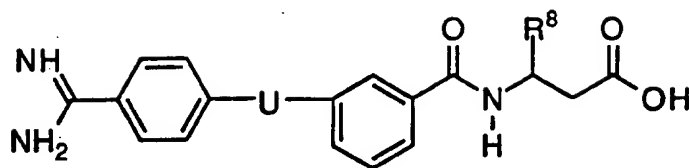
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Table 4a



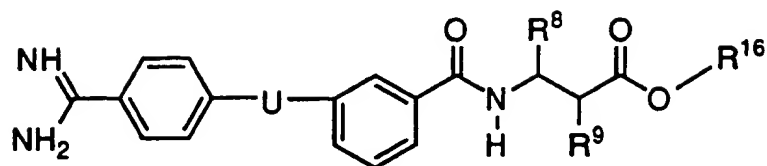
<u>Ex.</u> <u>No.</u>	<u>R¹-U</u>	<u>W</u>	<u>FAB MS</u> <u>(M+H)⁺</u>
480			389
481			403
482			375

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Table 5

<u>Example Number</u>	<u>U</u>	<u>R⁸</u>	<u>FAB MS (M+H)⁺</u>
85	OCH ₂	CH ₃	356.2
86	OCH ₂	CF ₃	
87	OCH ₂	C ₅ H ₅	
88	OCH ₂	2-pyridyl	
89	OCH ₂	3-pyridyl	
90	OCH ₂	4-pyridyl	
91	CH ₂ O	CH ₃	356.2
92	OCH ₂	CF ₃	410.2
93	CH ₂ O	C ₅ H ₅	
94	CH ₂ O	2-pyridyl	
95	CH ₂ O	3-pyridyl	
96	CH ₂ O	4-pyridyl	

Table 6



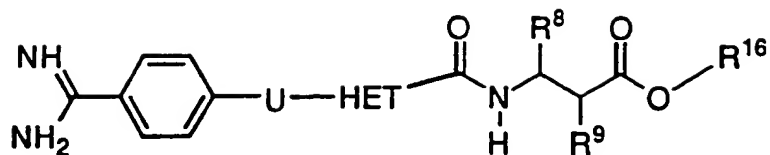
<u>Example Number</u>	<u>U</u>	<u>R⁹</u>	<u>R⁸</u>	<u>R¹⁶</u>	<u>FAB MS (M+H)⁺</u>
97	OCH ₂	CH ₃	H	CH ₃	
98	OCH ₂	CH ₃	H	CH ₂ CH ₃	
99	OCH ₂	C ₆ H ₅	H	CH ₃	
100	OCH ₂	C ₆ H ₅	H	CH ₂ CH ₃	
101	CH ₂ O	CH ₃	H	CH ₃	
102	CH ₂ O	CH ₃	H	CH ₂ CH ₃	
103	CH ₂ O	C ₆ H ₅	H	CH ₃	
104	CH ₂ O	C ₆ H ₅	H	CH ₂ CH ₃	
105	OCH ₂	NH-SO ₂ - 4-(methyl)phenyl	CH ₃	CH ₃	
106	OCH ₂	NH-SO ₂ - 4-(methyl)phenyl	H	CH ₂ CH ₃	
107	OCH ₂	NHSO ₂ (CH ₂) ₃ CH ₃	H	CH ₃	
108	OCH ₂	NHSO ₂ (CH ₂) ₃ CH ₃	H	CH ₂ CH ₃	
109	OCH ₂	NH-Cbz	H	CH ₃	
110	OCH ₂	NH-Cbz	H	CH ₂ CH ₃	
111	CH ₂ O	NH-SO ₂ - 4-(methyl)phenyl	CH ₃	CH ₃	
112	CH ₂ O	NH-SO ₂ -4- (methylphenyl)	H	CH ₂ CH ₃	
113	CH ₂ O	NHSO ₂ (CH ₂) ₃ CH ₃	H	CH ₃	

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<u>Example Number</u>	<u>U</u>	<u>R⁹</u>	<u>R⁸</u>	<u>R¹⁶</u>	<u>FAB MS (M+H)⁺</u>
114	CH ₂ O	NHSO ₂ (CH ₂) ₃ CH ₃	H	CH ₂ CH ₃	
115	CH ₂ O	NH-Cbz	H	CH ₃	
116	CH ₂ O	NH-Cbz	H	CH ₂ CH ₃	

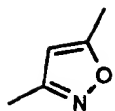
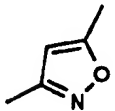
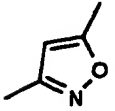
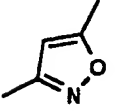
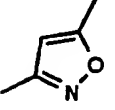
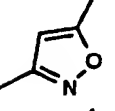
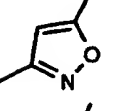
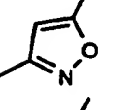
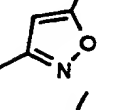
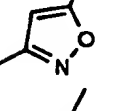
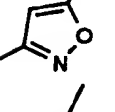
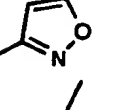
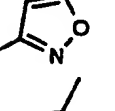
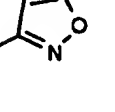
-147-

Table 7

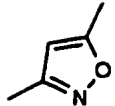
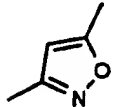
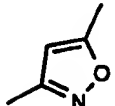
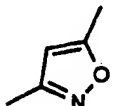
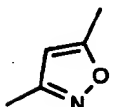
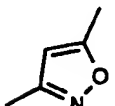
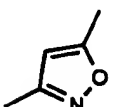
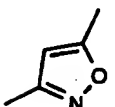
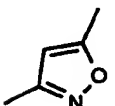
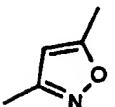
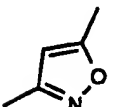
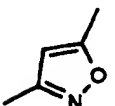
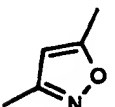
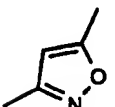


Ex. No.	U	HET	R ⁸	R ⁹	R ¹⁶
121	CH ₂ O		H	NHC(=O)OCH ₂ (C ₆ H ₅)	H
122	CH ₂ O		H	NHC(=O)OC(CH ₃) ₃	H
123	CH ₂ O		H	NHC(=O)O(CH ₂) ₃ CH ₃	H
124	CH ₂ O		H	NHC(=O)OCH ₂ CH ₃	H
125	CH ₂ O		H	NHC(=O)OCH ₃	H
126	CH ₂ O		H	NHC(=O)(CH ₂) ₂ -(C ₆ H ₅)	H
127	CH ₂ O		H	NHC(=O)CH ₂ C(CH ₃) ₃	H
128	CH ₂ O		H	NHC(=O)(CH ₂) ₄ CH ₃	H
129	CH ₂ O		H	NHC(=O)(CH ₂) ₃ CH ₃	H
130	CH ₂ O		H	NHC(=O)CH ₂ CH ₃	H
131	CH ₂ O		H	NHC(=O)-CH ₃	H
132	CH ₂ O		H	NHS(=O) ₂ CH ₂ CH ₃	H

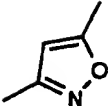
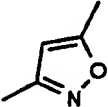
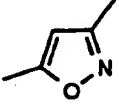
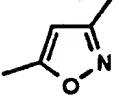
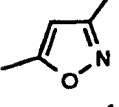
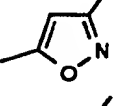
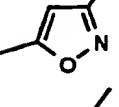
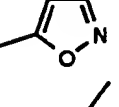
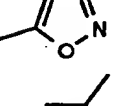
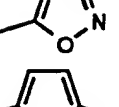
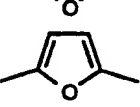
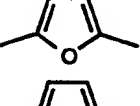
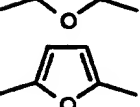
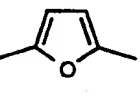


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133	CH ₂ O		H	NHS (=O) ₂ (CH ₂) ₃ CH ₃	H
134	CH ₂ O		H	NHS (=O) ₂ (C ₆ H ₅)	H
135	CH ₂ O		H	NHS (=O) ₂ -4-(methyl)phenyl	H
136	CH ₂ O		H	NHS (=O) ₂ CH ₂ (C ₆ H ₅)	H
137	CH ₂ O		H	NHC (=O)-2-pyridyl	H
138	CH ₂ O		H	NHC (=O)-3-pyridyl	H
139	CH ₂ O		H	NHC (=O)-4-pyridyl	H
140	CH ₂ O		H	NHC (=O)OCH ₂ (C ₆ H ₅)	Me
141	CH ₂ O		H	NHC (=O)OC(CH ₃) ₃	Me
142	CH ₂ O		H	NHC (=O)O(CH ₂) ₃ CH ₃	Me
143	CH ₂ O		H	NHC (=O)OCH ₂ CH ₃	Me
144	CH ₂ O		H	NHC (=O)OCH ₃	Me
145	CH ₂ O		H	NHC (=O)(CH ₂) ₂ -(C ₆ H ₅)	Me
146	CH ₂ O		H	NHC (=O)CH ₂ C(CH ₃) ₃	Me

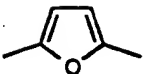
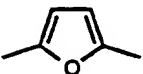
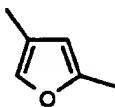
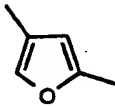
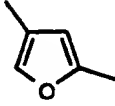
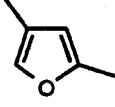
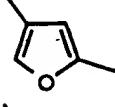
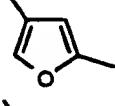
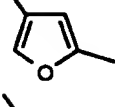
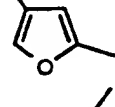
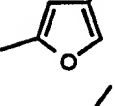
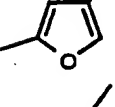
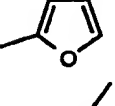
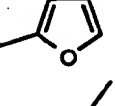
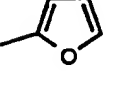
-149-

147	CH ₂ O		H	NHC(=O)(CH ₂) ₄ CH ₃	Me
148	CH ₂ O		H	NHC(=O)(CH ₂) ₃ CH ₃	Me
149	CH ₂ O		H	NHC(=O)CH ₂ CH ₃	Me
150	CH ₂ O		H	NHC(=O)-CH ₃	Me
151	CH ₂ O		H	NHS(=O) ₂ CH ₂ CH ₃	Me
152	CH ₂ O		H	NHS(=O) ₂ (CH ₂) ₃ CH ₃	Me
153	CH ₂ O		H	NHS(=O) ₂ (C ₆ H ₅)	Me
154	CH ₂ O		H	NHS(=O) ₂ -4-(methyl)phenyl	Me
155	CH ₂ O		H	NHS(=O) ₂ CH ₂ (C ₆ H ₅)	Me
156	CH ₂ O		H	NHC(=O)-2-pyridyl	Me
157	CH ₂ O		H	NHC(=O)-3-pyridyl	Me
158	CH ₂ O		H	NHC(=O)-4-pyridyl	Me
159	OCH ₂		H	NHC(=O)O(CH ₂) ₃ CH ₃	H
160	OCH ₂		H	NHS(=O) ₂ -4-(methyl)phenyl	H

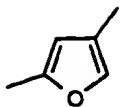
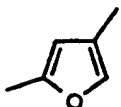
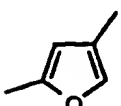
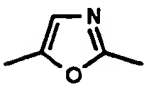
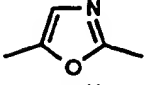
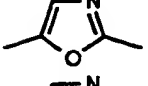
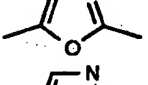
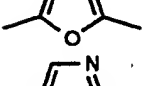
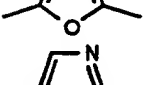
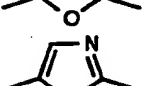
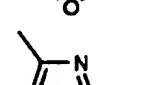
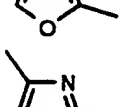
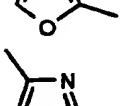
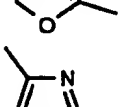
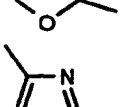
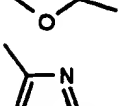
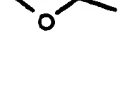
-150-

161	OCH ₂		H	NHC(=O)O(CH ₂) ₃ CH ₃	Me
162	OCH ₂		H	NHS(=O)2-4-(methyl)phenyl	Me
163	CH ₂ O		H	NHC(=O)O(CH ₂) ₃ CH ₃	H
164	CH ₂ O		H	NHS(=O)2-4-(methyl)phenyl	H
165	CH ₂ O		H	NHC(=O)O(CH ₂) ₃ CH ₃	Me
166	CH ₂ O		H	NHS(=O)2-4-(methyl)phenyl	Me
167	OCH ₂		H	NHC(=O)O(CH ₂) ₃ CH ₃	H
168	OCH ₂		H	NHS(=O)2-4-(methyl)phenyl	H
169	OCH ₂		H	NHC(=O)O(CH ₂) ₃ CH ₃	Me
170	OCH ₂		H	NHS(=O)2-4-(methyl)phenyl	Me
171	CH ₂ O		H	NHC(=O)O(CH ₂) ₃ CH ₃	H
172	CH ₂ O		H	NHS(=O)2-4-(methyl)phenyl	H
173	CH ₂ O		H	NHC(=O)O(CH ₂) ₃ CH ₃	Me
174	CH ₂ O		H	NHS(=O)2-4-(methyl)phenyl	Me
175	OCH ₂		H	NHC(=O)O(CH ₂) ₃ CH ₃	H
176	OCH ₂		H	NHS(=O)2-4-(methyl)phenyl	H

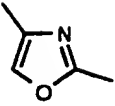
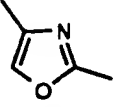
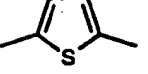
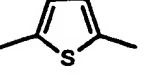
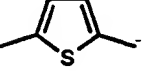
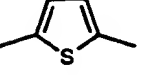
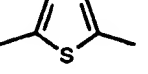
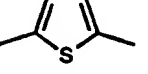
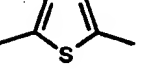
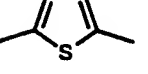
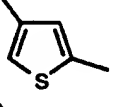
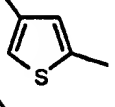
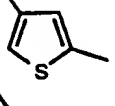
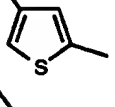
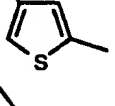
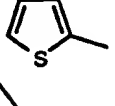
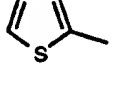
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177	OCH ₂		H	NHC(=O)O(CH ₂) ₃ CH ₃	Me
178	OCH ₂		H	NHS(=O)2-4-(methyl)phenyl	Me
179	CH ₂ O		H	NHC(=O)O(CH ₂) ₃ CH ₃	H
180	CH ₂ O		H	NHS(=O)2-4-(methyl)phenyl	H
181	CH ₂ O		H	NHC(=O)O(CH ₂) ₃ CH ₃	Me
182	CH ₂ O		H	NHS(=O)2-4-(methyl)phenyl	Me
183	OCH ₂		H	NHC(=O)O(CH ₂) ₃ CH ₃	H
184	OCH ₂		H	NHS(=O)2-4-(methyl)phenyl	H
185	OCH ₂		H	NHC(=O)O(CH ₂) ₃ CH ₃	Me
186	OCH ₂		H	NHS(=O)2-4-(methyl)phenyl	Me
187	CH ₂ O		H	NHC(=O)O(CH ₂) ₃ CH ₃	H
188	CH ₂ O		H	NHS(=O)2-4-(methyl)phenyl	H
189	CH ₂ O		H	NHC(=O)O(CH ₂) ₃ CH ₃	Me
190	CH ₂ O		H	NHS(=O)2-4-(methyl)phenyl	Me
191	OCH ₂		H	NHC(=O)O(CH ₂) ₃ CH ₃	H

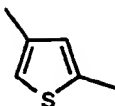
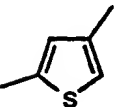
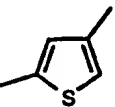
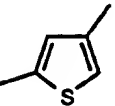
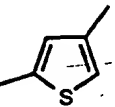
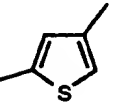
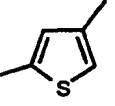
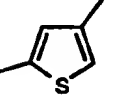
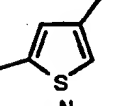
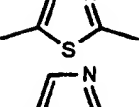
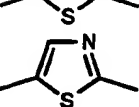
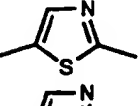
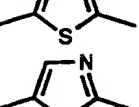
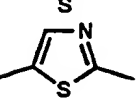


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192	OCH ₂		H	NHS (=O) 2-4-(methyl) phenyl	H
193	OCH ₂		H	NHC (=O) O (CH ₂) ₃ CH ₃	Me
194	OCH ₂		H	NHS (=O) 2-4-(methyl) phenyl	Me
195	CH ₂ O		H	NHC (=O) O (CH ₂) ₃ CH ₃	H
196	CH ₂ O		H	NHS (=O) 2-4-(methyl) phenyl	H
197	CH ₂ O		H	NHC (=O) O (CH ₂) ₃ CH ₃	Me
198	CH ₂ O		H	NHS (=O) 2-4-(methyl) phenyl	Me
199	OCH ₂		H	NHC (=O) O (CH ₂) ₃ CH ₃	H
200	OCH ₂		H	NHS (=O) 2-4-(methyl) phenyl	H
201	OCH ₂		H	NHC (=O) O (CH ₂) ₃ CH ₃	Me
202	OCH ₂		H	NHS (=O) 2-4-(methyl) phenyl	Me
203	CH ₂ O		H	NHC (=O) O (CH ₂) ₃ CH ₃	H
204	CH ₂ O		H	NHS (=O) 2-4-(methyl) phenyl	H
205	CH ₂ O		H	NHC (=O) O (CH ₂) ₃ CH ₃	Me
206	CH ₂ O		H	NHS (=O) 2-4-(methyl) phenyl	Me
207	OCH ₂		H	NHC (=O) O (CH ₂) ₃ CH ₃	H
208	OCH ₂		H	NHS (=O) 2-4-(methyl) phenyl	H

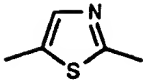
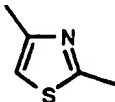
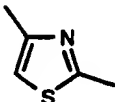
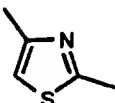
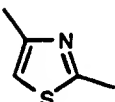
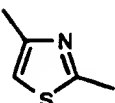
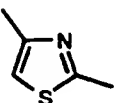
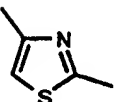
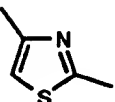
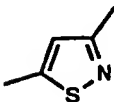
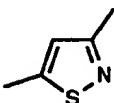
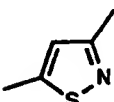
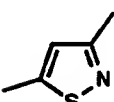
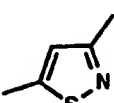
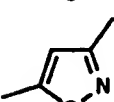
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209	OCH ₂		H	NHC(=O)O(CH ₂) ₃ CH ₃	Me
210	OCH ₂		H	NHS(=O)2-4-(methyl)phenyl	Me
211	CH ₂ O		H	NHC(=O)O(CH ₂) ₃ CH ₃	H
212	CH ₂ O		H	NHS(=O)2-4-(methyl)phenyl	H
213	CH ₂ O		H	NHC(=O)O(CH ₂) ₃ CH ₃	Me
214	CH ₂ O		H	NHS(=O)2-4-(methyl)phenyl	Me
215	OCH ₂		H	NHC(=O)O(CH ₂) ₃ CH ₃	H
216	OCH ₂		H	NHS(=O)2-4-(methyl)phenyl	H
217	OCH ₂		H	NHC(=O)O(CH ₂) ₃ CH ₃	Me
218	OCH ₂		H	NHS(=O)2-4-(methyl)phenyl	Me
219	CH ₂ O		H	NHC(=O)O(CH ₂) ₃ CH ₃	H
220	CH ₂ O		H	NHS(=O)2-4-(methyl)phenyl	H
221	CH ₂ O		H	NHC(=O)O(CH ₂) ₃ CH ₃	Me
222	CH ₂ O		H	NHS(=O)2-4-(methyl)phenyl	Me
223	OCH ₂		H	NHC(=O)O(CH ₂) ₃ CH ₃	H
224	OCH ₂		H	NHS(=O)2-4-(methyl)phenyl	H
225	OCH ₂		H	NHC(=O)O(CH ₂) ₃ CH ₃	Me

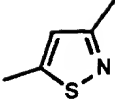
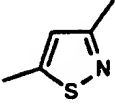
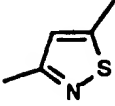
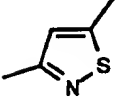
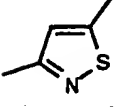
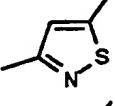
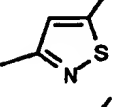
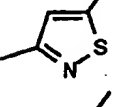
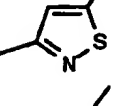
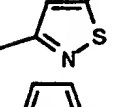
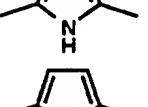
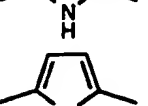
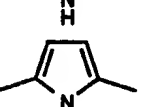
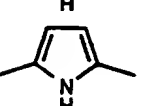

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Ex.No.	U	HET	R ⁸	R ⁹	R ¹⁶
226	OCH ₂		H	NHS (=O) 2-4-(methyl)phenyl	Me
227	CH ₂ O		H	NHC (=O) O (CH ₂) ₃ CH ₃	H
228	CH ₂ O		H	NHS (=O) 2-4-(methyl)phenyl	H
229	CH ₂ O		H	NHC (=O) O (CH ₂) ₃ CH ₃	Me
230	CH ₂ O		H	NHS (=O) 2-4-(methyl)phenyl	Me
231	OCH ₂		H	NHC (=O) O (CH ₂) ₃ CH ₃	H
232	OCH ₂		H	NHS (=O) 2-4-(methyl)phenyl	H
234	OCH ₂		H	NHC (=O) O (CH ₂) ₃ CH ₃	Me
235	OCH ₂		H	NHS (=O) 2-4-(methyl)phenyl	Me
236	CH ₂ O		H	NHC (=O) O (CH ₂) ₃ CH ₃	H
237	CH ₂ O		H	NHS (=O) 2-4-(methyl)phenyl	H
238	CH ₂ O		H	NHC (=O) O (CH ₂) ₃ CH ₃	Me
239	CH ₂ O		H	NHS (=O) 2-4-(methyl)phenyl	Me
240	OCH ₂		H	NHC (=O) O (CH ₂) ₃ CH ₃	H
242	OCH ₂		H	NHS (=O) 2-4-(methyl)phenyl	H
242	OCH ₂		H	NHC (=O) O (CH ₂) ₃ CH ₃	Me

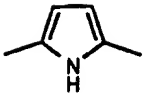
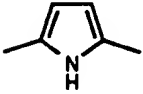
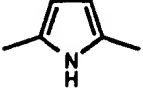
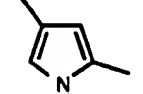
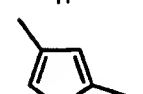
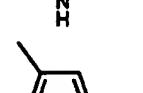
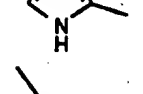
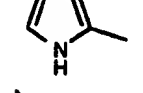
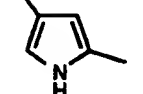
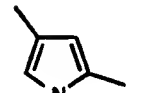
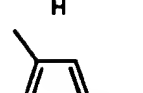
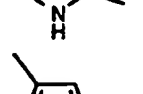
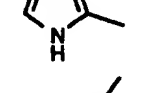
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243	OCH ₂		H	NHS (=O) 2-4-(methyl)phenyl	Me
244	CH ₂ O		H	NHC (=O) O (CH ₂) ₃ CH ₃	H
245	CH ₂ O		H	NHS (=O) 2-4-(methyl)phenyl	H
246	CH ₂ O		H	NHC (=O) O (CH ₂) ₃ CH ₃	Me
247	CH ₂ O		H	NHS (=O) 2-4-(methyl)phenyl	Me
248	OCH ₂		H	NHC (=O) O (CH ₂) ₃ CH ₃	H
249	OCH ₂		H	NHS (=O) 2-4-(methyl)phenyl	H
250	OCH ₂		H	NHC (=O) O (CH ₂) ₃ CH ₃	Me
251	OCH ₂		H	NHS (=O) 2-4-(methyl)phenyl	Me
252	CH ₂ O		H	NHC (=O) O (CH ₂) ₃ CH ₃	H
253	CH ₂ O		H	NHS (=O) 2-4-(methyl)phenyl	H
254	CH ₂ O		H	NHC (=O) O (CH ₂) ₃ CH ₃	Me
255	CH ₂ O		H	NHS (=O) 2-4-(methyl)phenyl	Me
256	OCH ₂		H	NHC (=O) O (CH ₂) ₃ CH ₃	H
257	OCH ₂		H	NHS (=O) 2-4-(methyl)phenyl	H

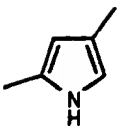
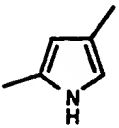
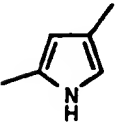
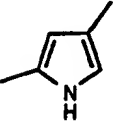
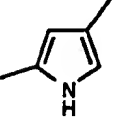
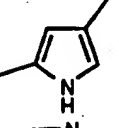
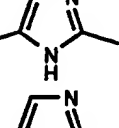
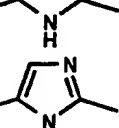
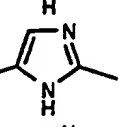
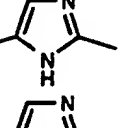
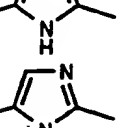
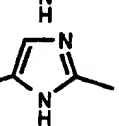


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258	OCH ₂		H	NHC(=O)O(CH ₂) ₃ CH ₃	Me
259	OCH ₂		H	NHS(=O)2-4-(methyl)phenyl	Me
260	CH ₂ O		H	NHC(=O)O(CH ₂) ₃ CH ₃	H
261	CH ₂ O		H	NHS(=O)2-4-(methyl)phenyl	H
262	CH ₂ O		H	NHC(=O)O(CH ₂) ₃ CH ₃	Me
263	CH ₂ O		H	NHS(=O)2-4-(methyl)phenyl	Me
264	OCH ₂		H	NHC(=O)O(CH ₂) ₃ CH ₃	H
265	OCH ₂		H	NHS(=O)2-4-(methyl)phenyl	H
266	OCH ₂		H	NHC(=O)O(CH ₂) ₃ CH ₃	Me
267	OCH ₂		H	NHS(=O)2-4-(methyl)phenyl	Me
268	CH ₂ O		H	NHC(=O)O(CH ₂) ₃ CH ₃	H
269	CH ₂ O		H	NHS(=O)2-4-(methyl)phenyl	H
270	CH ₂ O		H	NHC(=O)O(CH ₂) ₃ CH ₃	Me
271	CH ₂ O		H	NHS(=O)2-4-(methyl)phenyl	Me
272	OCH ₂		H	NHC(=O)O(CH ₂) ₃ CH ₃	H

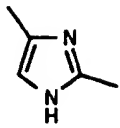
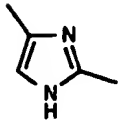
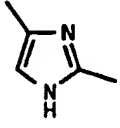
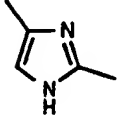
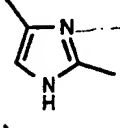
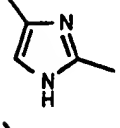
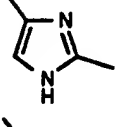
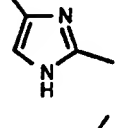
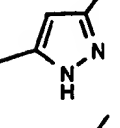
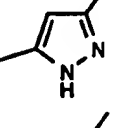
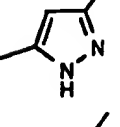
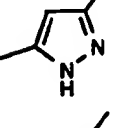
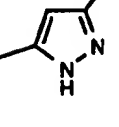
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273	OCH ₂		H	NHS (=O) 2-4-(methyl)phenyl	H
274	OCH ₂		H	NHC (=O) O (CH ₂) ₃ CH ₃	Me
275	OCH ₂		H	NHS (=O) 2-4-(methyl)phenyl	Me
276	CH ₂ O		H	NHC (=O) O (CH ₂) ₃ CH ₃	H
277	CH ₂ O		H	NHS (=O) 2-4-(methyl)phenyl	H
278	CH ₂ O		H	NHC (=O) O (CH ₂) ₃ CH ₃	Me
279	CH ₂ O		H	NHS (=O) 2-4-(methyl)phenyl	Me
280	OCH ₂		H	NHC (=O) O (CH ₂) ₃ CH ₃	H
281	OCH ₂		H	NHS (=O) 2-4-(methyl)phenyl	H
282	OCH ₂		H	NHC (=O) O (CH ₂) ₃ CH ₃	Me
283	OCH ₂		H	NHS (=O) 2-4-(methyl)phenyl	Me
284	CH ₂ O		H	NHC (=O) O (CH ₂) ₃ CH ₃	H
285	CH ₂ O		H	NHS (=O) 2-4-(methyl)phenyl	H

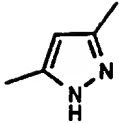
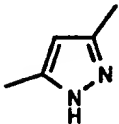
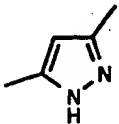
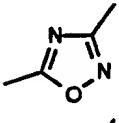
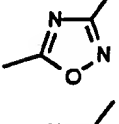
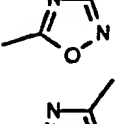
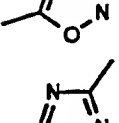
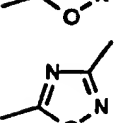
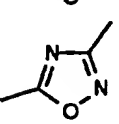
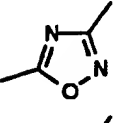
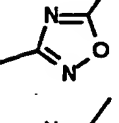
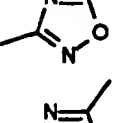
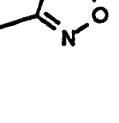

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286	CH ₂ O		H	NHC(=O)O(CH ₂) ₃ CH ₃	Me
287	CH ₂ O		H	NHS(=O)2-4-(methyl)phenyl	Me
288	OCH ₂		H	NHC(=O)O(CH ₂) ₃ CH ₃	H
289	OCH ₂		H	NHS(=O)2-4-(methyl)phenyl	H
290	OCH ₂		H	NHC(=O)O(CH ₂) ₃ CH ₃	Me
291	OCH ₂		H	NHS(=O)2-4-(methyl)phenyl	Me
292	CH ₂ O		H	NHC(=O)O(CH ₂) ₃ CH ₃	H
293	CH ₂ O		H	NHS(=O)2-4-(methyl)phenyl	H
294	CH ₂ O		H	NHC(=O)O(CH ₂) ₃ CH ₃	Me
295	CH ₂ O		H	NHS(=O)2-4-(methyl)phenyl	Me
296	OCH ₂		H	NHC(=O)O(CH ₂) ₃ CH ₃	H
297	OCH ₂		H	NHS(=O)2-4-(methyl)phenyl	H
298	OCH ₂		H	NHC(=O)O(CH ₂) ₃ CH ₃	Me
299	OCH ₂		H	NHS(=O)2-4-(methyl)phenyl	Me

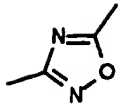
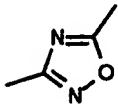
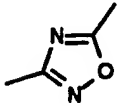
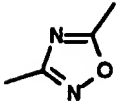
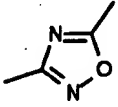
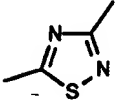
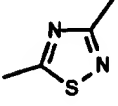
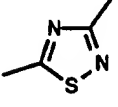
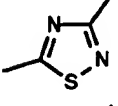
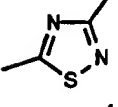
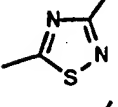
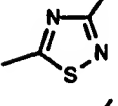
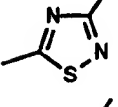
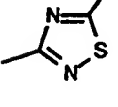
-159-

300	CH ₂ O		H	NHC(=O)O(CH ₂) ₃ CH ₃	H
301	CH ₂ O		H	NHS(=O)2-4-(methyl)phenyl	H
302	CH ₂ O		H	NHC(=O)O(CH ₂) ₃ CH ₃	Me
303	CH ₂ O		H	NHS(=O)2-4-(methyl)phenyl	Me
304	OCH ₂		H	NHC(=O)O(CH ₂) ₃ CH ₃	H
305	OCH ₂		H	NHS(=O)2-4-(methyl)phenyl	H
306	OCH ₂		H	NHC(=O)O(CH ₂) ₃ CH ₃	Me
307	OCH ₂		H	NHS(=O)2-4-(methyl)phenyl	Me
308	CH ₂ O		H	NHC(=O)O(CH ₂) ₃ CH ₃	H
309	CH ₂ O		H	NHS(=O)2-4-(methyl)phenyl	H
310	CH ₂ O		H	NHC(=O)O(CH ₂) ₃ CH ₃	Me
311	CH ₂ O		H	NHS(=O)2-4-(methyl)phenyl	Me
312	OCH ₂		H	NHC(=O)O(CH ₂) ₃ CH ₃	H

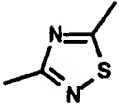
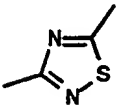
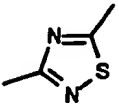
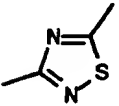
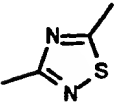
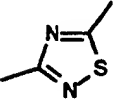
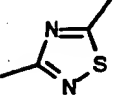
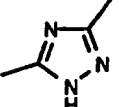
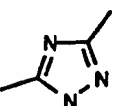
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313	OCH ₂		H	NHS (=O) 2-4-(methyl)phenyl	H
314	OCH ₂		H	NHC (=O) O (CH ₂) ₃ CH ₃	Me
315	OCH ₂		H	NHS (=O) 2-4-(methyl)phenyl	Me
316	CH ₂ O		H	NHC (=O) O (CH ₂) ₃ CH ₃	H
317	CH ₂ O		H	NHS (=O) 2-4-(methyl)phenyl	H
318	CH ₂ O		H	NHC (=O) O (CH ₂) ₃ CH ₃	Me
319	CH ₂ O		H	NHS (=O) 2-4-(methyl)phenyl	Me
320	OCH ₂		H	NHC (=O) O (CH ₂) ₃ CH ₃	H
321	OCH ₂		H	NHS (=O) 2-4-(methyl)phenyl	H
322	OCH ₂		H	NHC (=O) O (CH ₂) ₃ CH ₃	Me
323	OCH ₂		H	NHS (=O) 2-4-(methyl)phenyl	Me
324	CH ₂ O		H	NHC (=O) O (CH ₂) ₃ CH ₃	H
325	CH ₂ O		H	NHS (=O) 2-4-(methyl)phenyl	H
326	CH ₂ O		H	NHC (=O) O (CH ₂) ₃ CH ₃	Me

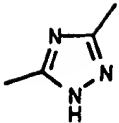
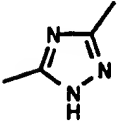
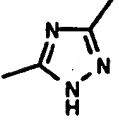
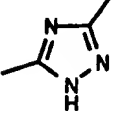
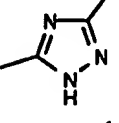
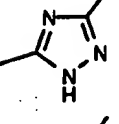
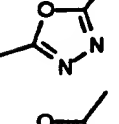
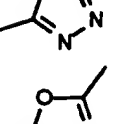
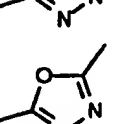
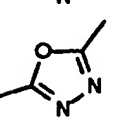
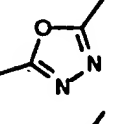
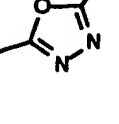

-161-

327	CH ₂ O		H	NHS (=O) 2-4-(methyl)phenyl	Me
328	OCH ₂		H	NHC (=O) O (CH ₂) ₃ CH ₃	H
329	OCH ₂		H	NHS (=O) 2-4-(methyl)phenyl	H
330	OCH ₂		H	NHC (=O) O (CH ₂) ₃ CH ₃	Me
331	OCH ₂		H	NHS (=O) 2-4-(methyl)phenyl	Me
332	CH ₂ O		H	NHC (=O) O (CH ₂) ₃ CH ₃	H
333	CH ₂ O		H	NHS (=O) 2-4-(methyl)phenyl	H
334	CH ₂ O		H	NHC (=O) O (CH ₂) ₃ CH ₃	Me
335	CH ₂ O		H	NHS (=O) 2-4-(methyl)phenyl	Me
336	OCH ₂		H	NHC (=O) O (CH ₂) ₃ CH ₃	H
337	OCH ₂		H	NHS (=O) 2-4-(methyl)phenyl	H
338	OCH ₂		H	NHC (=O) O (CH ₂) ₃ CH ₃	Me
339	OCH ₂		H	NHS (=O) 2-4-(methyl)phenyl	Me
340	CH ₂ O		H	NHC (=O) O (CH ₂) ₃ CH ₃	H

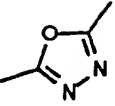
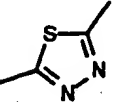
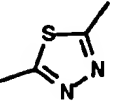
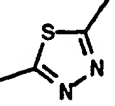
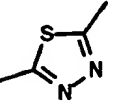
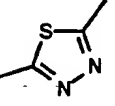
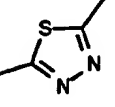
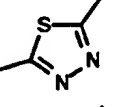
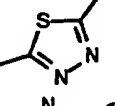
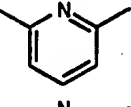
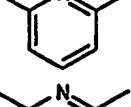
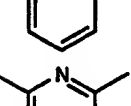
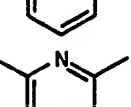
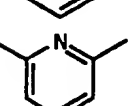

-162-

341	CH ₂ O		H	NHS (=O) 2-4- (methyl) phenyl	H
342	CH ₂ O		H	NHC (=O) O (CH ₂) ₃ CH ₃	Me
343	CH ₂ O		H	NHS (=O) 2-4- (methyl) phenyl	Me
345	OCH ₂		H	NHC (=O) O (CH ₂) ₃ CH ₃	H
346	OCH ₂		H	NHS (=O) 2-4- (methyl) phenyl	H
347	OCH ₂		H	NHC (=O) O (CH ₂) ₃ CH ₃	Me
348	OCH ₂		H	NHS (=O) 2-4- (methyl) phenyl	Me
349	CH ₂ O		H	NHC (=O) O (CH ₂) ₃ CH ₃	H
350	CH ₂ O		H	NHS (=O) 2-4- (methyl) phenyl	H

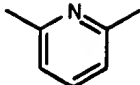
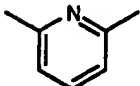
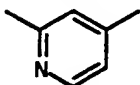
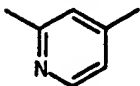
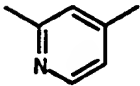
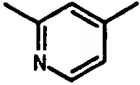
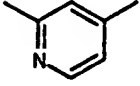
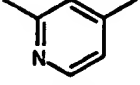
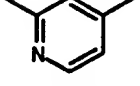
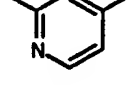
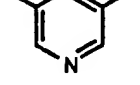
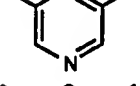
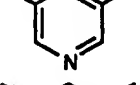
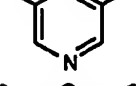
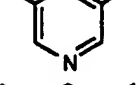
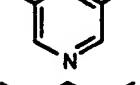
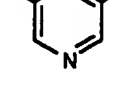
-163-

351	CH ₂ O		H	NHC(=O)O(CH ₂) ₃ CH ₃	Me
352	CH ₂ O		H	NHS(=O)2-4-(methyl)phenyl	Me
353	OCH ₂		H	NHC(=O)O(CH ₂) ₃ CH ₃	H
354	OCH ₂		H	NHS(=O)2-4-(methyl)phenyl	H
356	OCH ₂		H	NHC(=O)O(CH ₂) ₃ CH ₃	Me
357	OCH ₂		H	NHS(=O)2-4-(methyl)phenyl	Me
358	CH ₂ O		H	NHC(=O)O(CH ₂) ₃ CH ₃	H
359	CH ₂ O		H	NHS(=O)2-4-(methyl)phenyl	H
360	CH ₂ O		H	NHC(=O)O(CH ₂) ₃ CH ₃	Me
361	CH ₂ O		H	NHS(=O)2-4-(methyl)phenyl	Me
362	OCH ₂		H	NHC(=O)O(CH ₂) ₃ CH ₃	H
363	OCH ₂		H	NHS(=O)2-4-(methyl)phenyl	H
364	OCH ₂		H	NHC(=O)O(CH ₂) ₃ CH ₃	Me

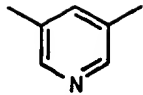
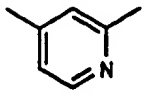
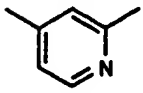
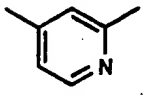
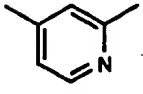
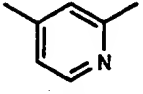
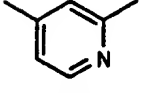
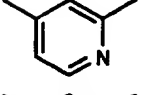
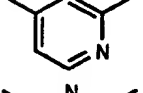
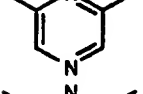
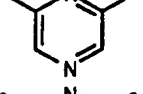
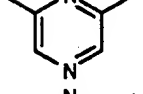
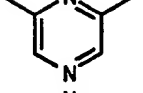
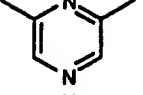
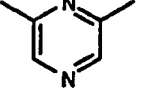
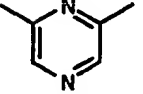
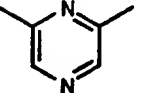
-164-

365	OCH ₂		H	NHS (=O) 2-4-(methyl)phenyl	Me
366	CH ₂ O		H	NHC (=O) O (CH ₂) ₃ CH ₃	H
367	CH ₂ O		H	NHS (=O) 2-4-(methyl)phenyl	H
368	CH ₂ O		H	NHC (=O) O (CH ₂) ₃ CH ₃	Me
369	CH ₂ O		H	NHS (=O) 2-4-(methyl)phenyl	Me
370	OCH ₂		H	NHC (=O) O (CH ₂) ₃ CH ₃	H
371	OCH ₂		H	NHS (=O) 2-4-(methyl)phenyl	H
372	OCH ₂		H	NHC (=O) O (CH ₂) ₃ CH ₃	Me
373	OCH ₂		H	NHS (=O) 2-4-(methyl)phenyl	Me
374	CH ₂ O		H	NHC (=O) O (CH ₂) ₃ CH ₃	H
375	CH ₂ O		H	NHS (=O) 2-4-(methyl)phenyl	H
376	CH ₂ O		H	NHC (=O) O (CH ₂) ₃ CH ₃	Me
377	CH ₂ O		H	NHS (=O) 2-4-(methyl)phenyl	Me
378	OCH ₂		H	NHC (=O) O (CH ₂) ₃ CH ₃	H
379	OCH ₂		H	NHS (=O) 2-4-(methyl)phenyl	H

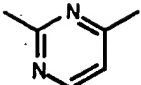
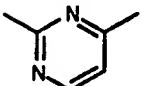
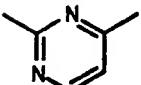
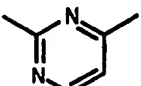
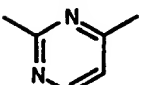
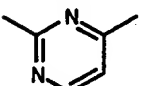
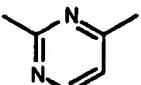
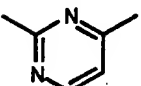
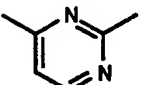
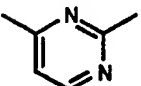
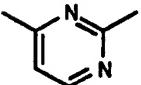
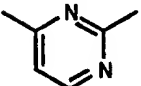
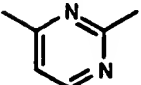
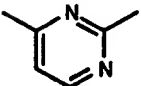
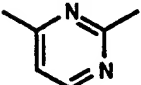
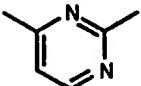
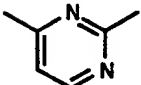
-165-

380	OCH ₂		H	NHC(=O)O(CH ₂) ₃ CH ₃	Me
381	OCH ₂		H	NHS(=O)2-4-(methyl)phenyl	Me
382	CH ₂ O		H	NHC(=O)O(CH ₂) ₃ CH ₃	H
383	CH ₂ O		H	NHS(=O)2-4-(methyl)phenyl	H
384	CH ₂ O		H	NHC(=O)O(CH ₂) ₃ CH ₃	Me
385	CH ₂ O		H	NHS(=O)2-4-(methyl)phenyl	Me
386	OCH ₂		H	NHC(=O)O(CH ₂) ₃ CH ₃	H
387	OCH ₂		H	NHS(=O)2-4-(methyl)phenyl	H
388	OCH ₂		H	NHC(=O)O(CH ₂) ₃ CH ₃	Me
389	OCH ₂		H	NHS(=O)2-4-(methyl)phenyl	Me
390	CH ₂ O		H	NHC(=O)O(CH ₂) ₃ CH ₃	H
391	CH ₂ O		H	NHS(=O)2-4-(methyl)phenyl	H
392	CH ₂ O		H	NHC(=O)O(CH ₂) ₃ CH ₃	Me
393	CH ₂ O		H	NHS(=O)2-4-(methyl)phenyl	Me
394	OCH ₂		H	NHC(=O)O(CH ₂) ₃ CH ₃	H
395	OCH ₂		H	NHS(=O)2-4-(methyl)phenyl	H
396	OCH ₂		H	NHC(=O)O(CH ₂) ₃ CH ₃	Me

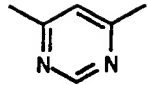
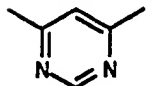
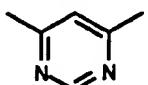
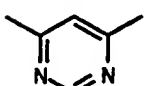
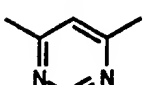
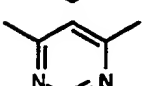
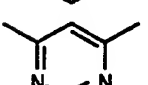
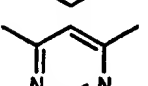
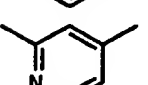
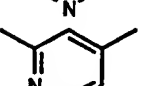
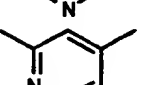
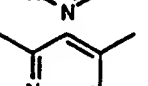
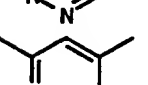
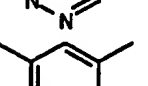
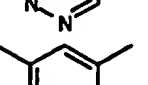
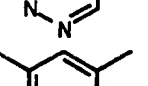
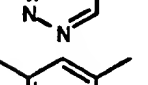
-166-

397	OCH ₂		H	NHS (=O) 2-4-(methyl)phenyl	Me
398	CH ₂ O		H	NHC (=O) O (CH ₂) ₃ CH ₃	H
399	CH ₂ O		H	NHS (=O) 2-4-(methyl)phenyl	H
400	CH ₂ O		H	NHC (=O) O (CH ₂) ₃ CH ₃	Me
401	CH ₂ O		H	NHS (=O) 2-4-(methyl)phenyl	Me
402	OCH ₂		H	NHC (=O) O (CH ₂) ₃ CH ₃	H
403	OCH ₂		H	NHS (=O) 2-4-(methyl)phenyl	H
404	OCH ₂		H	NHC (=O) O (CH ₂) ₃ CH ₃	Me
405	OCH ₂		H	NHS (=O) 2-4-(methyl)phenyl	Me
406	CH ₂ O		H	NHC (=O) O (CH ₂) ₃ CH ₃	H
407	CH ₂ O		H	NHS (=O) 2-4-(methyl)phenyl	H
408	CH ₂ O		H	NHC (=O) O (CH ₂) ₃ CH ₃	Me
409	CH ₂ O		H	NHS (=O) 2-4-(methyl)phenyl	Me
410	OCH ₂		H	NHC (=O) O (CH ₂) ₃ CH ₃	H
411	OCH ₂		H	NHS (=O) 2-4-(methyl)phenyl	H
412	OCH ₂		H	NHC (=O) O (CH ₂) ₃ CH ₃	Me
413	OCH ₂		H	NHS (=O) 2-4-(methyl)phenyl	Me

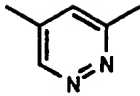
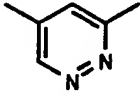
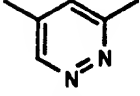
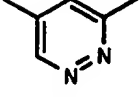
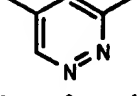
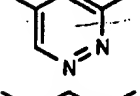
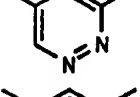
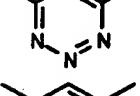
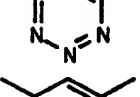
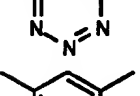
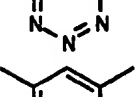
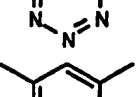
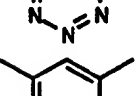
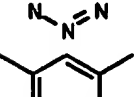
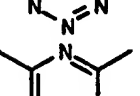
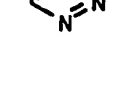
-167-

414	CH ₂ O		H	NHS (=O) 2-4-(methyl)phenyl	Me
415	CH ₂ O		H	NHC (=O) O (CH ₂) ₃ CH ₃	H
416	CH ₂ O		H	NHS (=O) 2-4-(methyl)phenyl	H
417	CH ₂ O		H	NHC (=O) O (CH ₂) ₃ CH ₃	Me
418	OCH ₂		H	NHS (=O) 2-4-(methyl)phenyl	Me
419	OCH ₂		H	NHC (=O) O (CH ₂) ₃ CH ₃	H
420	OCH ₂		H	NHS (=O) 2-4-(methyl)phenyl	H
421	OCH ₂		H	NHC (=O) O (CH ₂) ₃ CH ₃	Me
422	OCH ₂		H	NHS (=O) 2-4-(methyl)phenyl	Me
423	CH ₂ O		H	NHC (=O) O (CH ₂) ₃ CH ₃	H
424	CH ₂ O		H	NHS (=O) 2-4-(methyl)phenyl	H
425	CH ₂ O		H	NHC (=O) O (CH ₂) ₃ CH ₃	Me
426	CH ₂ O		H	NHS (=O) 2-4-(methyl)phenyl	Me
427	OCH ₂		H	NHC (=O) O (CH ₂) ₃ CH ₃	H
428	OCH ₂		H	NHS (=O) 2-4-(methyl)phenyl	H
429	OCH ₂		H	NHC (=O) O (CH ₂) ₃ CH ₃	Me
430	OCH ₂		H	NHS (=O) 2-4-(methyl)phenyl	Me

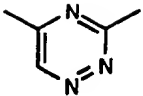
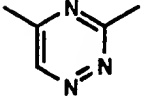
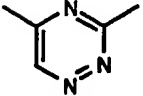
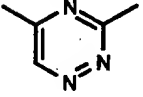
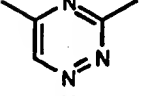
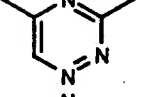
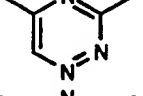
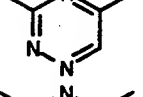
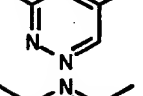
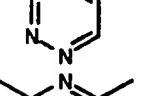
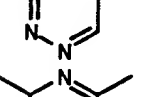
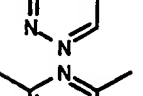
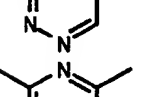
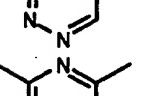
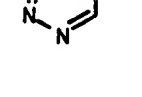
-168-

431	CH ₂ O		H	NHC(=O)O(CH ₂) ₃ CH ₃	H
432	CH ₂ O		H	NHS(=O)2-4-(methyl)phenyl	H
433	CH ₂ O		H	NHC(=O)O(CH ₂) ₃ CH ₃	Me
434	CH ₂ O		H	NHS(=O)2-4-(methyl)phenyl	Me
435	OCH ₂		H	NHC(=O)O(CH ₂) ₃ CH ₃	H
436	OCH ₂		H	NHS(=O)2-4-(methyl)phenyl	H
437	OCH ₂		H	NHC(=O)O(CH ₂) ₃ CH ₃	Me
438	OCH ₂		H	NHS(=O)2-4-(methyl)phenyl	Me
439	CH ₂ O		H	NHC(=O)O(CH ₂) ₃ CH ₃	H
440	CH ₂ O		H	NHS(=O)2-4-(methyl)phenyl	H
441	CH ₂ O		H	NHC(=O)O(CH ₂) ₃ CH ₃	Me
442	CH ₂ O		H	NHS(=O)2-4-(methyl)phenyl	Me
443	OCH ₂		H	NHC(=O)O(CH ₂) ₃ CH ₃	H
444	OCH ₂		H	NHS(=O)2-4-(methyl)phenyl	H
445	OCH ₂		H	NHC(=O)O(CH ₂) ₃ CH ₃	Me
446	OCH ₂		H	NHS(=O)2-4-(methyl)phenyl	Me
447	CH ₂ O		H	NHC(=O)O(CH ₂) ₃ CH ₃	H

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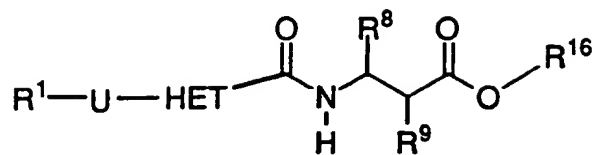
448	CH ₂ O		H	NHS (=O) 2-4-(methyl)phenyl	H
449	CH ₂ O		H	NHC (=O) O (CH ₂) ₃ CH ₃	Me
450	CH ₂ O		H	NHS (=O) 2-4-(methyl)phenyl	Me
451	OCH ₂		H	NHC (=O) O (CH ₂) ₃ CH ₃	H
452	OCH ₂		H	NHS (=O) 2-4-(methyl)phenyl	H
453	OCH ₂		H	NHC (=O) O (CH ₂) ₃ CH ₃	Me
454	OCH ₂		H	NHS (=O) 2-4-(methyl)phenyl	Me
455	CH ₂ O		H	NHC (=O) O (CH ₂) ₃ CH ₃	H
456	CH ₂ O		H	NHS (=O) 2-4-(methyl)phenyl	H
457	CH ₂ O		H	NHC (=O) O (CH ₂) ₃ CH ₃	Me
458	CH ₂ O		H	NHS (=O) 2-4-(methyl)phenyl	Me
459	OCH ₂		H	NHC (=O) O (CH ₂) ₃ CH ₃	H
460	OCH ₂		H	NHS (=O) 2-4-(methyl)phenyl	H
461	OCH ₂		H	NHC (=O) O (CH ₂) ₃ CH ₃	Me
462	OCH ₂		H	NHS (=O) 2-4-(methyl)phenyl	Me
463	CH ₂ O		H	NHC (=O) O (CH ₂) ₃ CH ₃	H

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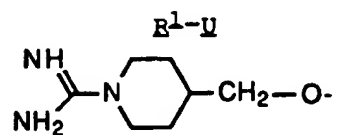
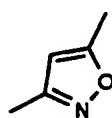
464	CH ₂ O		H	NHS (=O) 2-4-(methyl)phenyl	H
465	CH ₂ O		H	NHC (=O) O (CH ₂) ₃ CH ₃	Me
466	CH ₂ O		H	NHS (=O) 2-4-(methyl)phenyl	Me
467	OCH ₂		H	NHC (=O) O (CH ₂) ₃ CH ₃	H
468	OCH ₂		H	NHS (=O) 2-4-(methyl)phenyl	H
469	OCH ₂		H	NHC (=O) O (CH ₂) ₃ CH ₃	Me
470	OCH ₂		H	NHS (=O) 2-4-(methyl)phenyl	Me
471	CH ₂ O		H	NHC (=O) O (CH ₂) ₃ CH ₃	H
472	CH ₂ O		H	NHS (=O) 2-4-(methyl)phenyl	H
473	CH ₂ O		H	NHC (=O) O (CH ₂) ₃ CH ₃	Me
474	CH ₂ O		H	NHS (=O) 2-4-(methyl)phenyl	Me
475	OCH ₂		H	NHC (=O) O (CH ₂) ₃ CH ₃	H
476	OCH ₂		H	NHS (=O) 2-4-(methyl)phenyl	H
477	OCH ₂		H	NHC (=O) O (CH ₂) ₃ CH ₃	Me
478	OCH ₂		H	NHS (=O) 2-4-(methyl)phenyl	Me

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Table 8

Ex. No

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HETR⁸

H

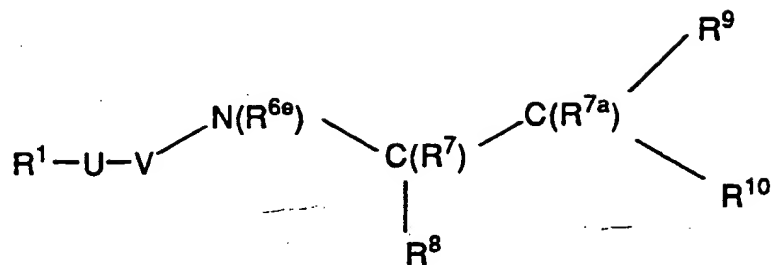
R⁹NHCO₂nBuR¹⁶

Me

CLAIMS

5 WHAT IS CLAIMED IS:

1. A compound of Formula I:



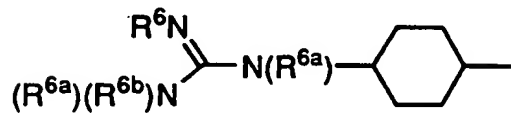
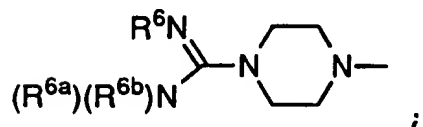
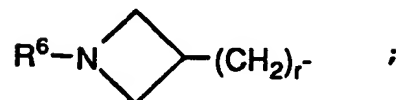
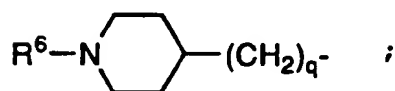
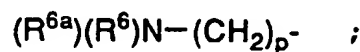
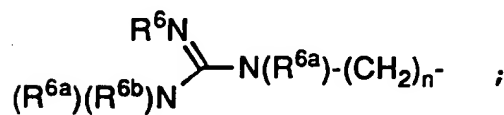
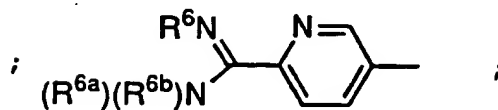
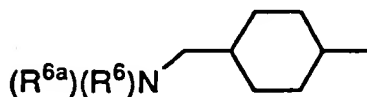
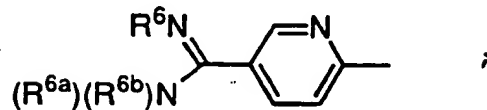
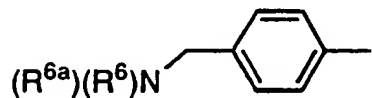
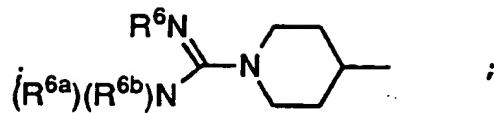
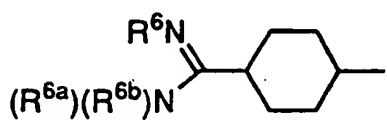
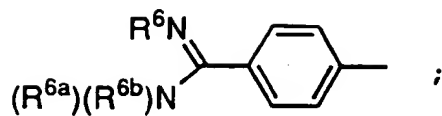
10

(I)

or a pharmaceutically acceptable salt form thereof
wherein:

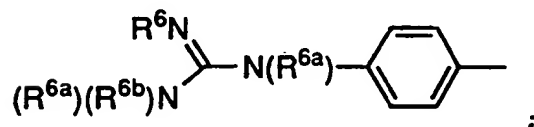
15 R¹ is selected from:

-173-



5

; or



n is 2, 3, or 4;

-174-

p is 4, 5, or 6;

q is 1, 2, or 3;

5 r is 2, 3, or 4;

R⁶ and R^{6a} are independently selected from: H, C₁-C₁₀ alkyl, C₂-C₆ alkenyl, C₃-C₁₁ cycloalkyl, C₄-C₁₁ cycloalkylalkyl, aryl, aryl(C₁-C₆ alkyl)-, (C₁-C₇ alkyl)carbonyl, arylcarbonyl, (C₁-C₁₀ alkoxy)carbonyl, C₄-C₁₁ cycloalkoxycarbonyl, C₇-C₁₁ bicycloalkoxycarbonyl, aryloxycarbonyl, aryl(C₁-C₁₀ alkyl)carbonyl, or aryl(C₁-C₁₀ alkoxy)carbonyl;

15

R⁷ and R^{7a} are selected independently from: H or C₁-C₄ alkyl;

R^{6b} is selected from: H, C₁-C₁₀ alkyl, C₂-C₆ alkenyl, C₃-C₁₁ cycloalkyl, C₄-C₁₅ cycloalkylalkyl, aryl, aryl(C₁-C₁₀ alkyl)-;

20

R^{6e} is selected from: H, C₁-C₁₀ alkyl, C₂-C₆ alkenyl, C₃-C₁₁ cycloalkyl, C₄-C₁₅ cycloalkylalkyl, aryl, aryl(C₁-C₁₀ alkyl)-;

25

alternatively, R^{6e} and R⁷ can be taken together with the nitrogen and carbon atom to which they are attached to form a 5-7 membered nitrogen heterocycle, said heterocycle optionally including one additional N, O or S atom;

30

U is selected from:

-CH₂-CH₂-CH₂- substituted with 0-4 R³,
-X-CH₂-CH₂- substituted with 0-4 R³,
-CH₂-X-CH₂- substituted with 0-4 R³,
-CH₂-CH₂-X- substituted with 0-4 R³,

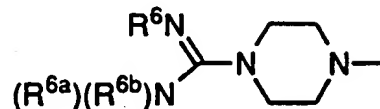
35

-175-

- CH₂-CH=CH- substituted with 0-4 R³,
 -CH=CH-CH₂- substituted with 0-4 R³,
 -CH₂-C≡C- substituted with 0-2 R³,
 -C≡C-CH₂- substituted with 0-2 R³,
 5 -CH=CH- substituted with 0-2 R³,
 -C≡C-,
 -CH₂-CH₂- substituted with 0-4 R³,
 -X-CH₂- substituted with 0-2 R³,
 -CH₂-X- substituted with 0-2 R³,
 10 -X-, or
 -CH₂- substituted with 0-2 R³;

- X is selected from: O, S, S(=O), SO₂, SO₂N(R^{6c}),
 N(R^{6c})SO₂, N(R^{6c}), N(R¹²), C(=O)N(R^{6c}),
 15 N(R^{6c})C(=O);

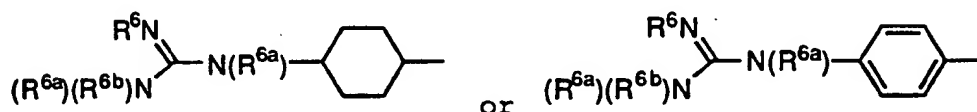
with the proviso that when R¹ is



then X is not S, S(=O), or SO₂N(R^{6c});

20

with the further proviso that when R¹ is



- then U is not optionally substituted -CH₂-CH₂-CH₂-,
 25 -X-CH₂-CH₂-, -CH₂-X-CH₂-, -CH₂-CH₂-X-, -CH₂-CH=CH-,
 -CH=CH-CH₂-, -CH₂-C≡C-, or -C≡C-CH₂-;

- R¹² and R¹³ are independently selected from: H, C₁-C₁₀
 alkyl, C₁-C₁₀ alkoxy carbonyl, C₁-C₁₀ alkyl carbonyl,
 30 C₁-C₁₀ alkylsulfonyl, aryl(C₁-C₁₀ alkyl)sulfonyl,
 arylsulfonyl, aryl, C₂-C₆ alkenyl, C₃-C₁₁
 cycloalkyl, C₄-C₁₅ cycloalkylalkyl,
 aryl(C₁-C₁₀ alkyl), aryl carbonyl, C₄-C₁₁

-176-

cycloalkoxycarbonyl, C7-C11 bicycloalkoxycarbonyl,
aryloxycarbonyl, or aryl(C1-C10 alkoxy)carbonyl;

5 R^{6c} is selected from: H, C1-C10 alkyl, C2-C6 alkenyl,
C3-C11 cycloalkyl, C4-C15 cycloalkylalkyl, aryl,
aryl(C1-C10 alkyl)-;

10 R³ is independently selected from: H, C1-C6 alkyl, C3-C6
cycloalkyl, C4-C11 cycloalkylalkyl, aryl,
aryl(C1-C6 alkyl)-;

V is -Q-Y-;

15 Q is a 5- membered heterocyclic ring system having 1-4
heteroatoms selected independently from O, S, and
N, said heterocyclic ring being substituted with
0-2 R⁵;

20 Y is selected from: C(=O) or S(O)₂;

R⁵ is selected independently from: H, F, Cl, Br, I, CF₃,
CN, CHO, CO₂R^{5a}, C(=O)R^{5a}, CONHR^{5a}, CON(R^{5a})₂,
OC(=O)R^{5a}, OCO₂R^{5a}, OR^{5a}, OC(=O)N(R^{5a})₂, OCH₂CO₂R^{5a},
CO₂CH₂CO₂R^{5a}, N(R¹²)R^{5a}, NO₂, NR^{5a}C(=O)R^{5a},
25 NR^{5a}C(=O)OR^{5a}, NR^{5a}SO₂N(R¹²)R^{5a}, NR^{5a}SO₂R^{5b}, SR^{5a},
S(=O)R^{5b}, SO₂R^{5b}, SO₂N(R^{5a})₂, C1 to C10 alkyl, C2
to C6 alkenyl, C2 to C6 alkynyl, C3 to C11
cycloalkyl, C4 to C15 cycloalkylalkyl, aryl,
aryl(C1-C10 alkyl),

30 C1 to C6 alkyl substituted with 0-4 R^{5c},
C2 to C6 alkenyl substituted with 0-4 R^{5c},
C2 to C6 alkynyl substituted with 0-4 R^{5c},
C3 to C11 cycloalkyl substituted with 0-3 R^{5c},
35 C4 to C15 cycloalkylalkyl substituted with 0-3 R^{5c},
aryl substituted with 0-3 R^{5c},
aryl(C1-C10 alkyl) substituted with 0-3 R^{5c};

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R^{5a} is selected from: H, C₁ to C₁₀ alkyl, C₂ to C₆ alkenyl, C₃ to C₁₁ cycloalkyl, C₄ to C₁₅ cycloalkylalkyl, aryl, or aryl(C₁-C₁₀ alkyl);

5

R^{5b} is selected from: C₁ to C₁₀ alkyl, C₂ to C₆ alkenyl, C₃ to C₁₅ cycloalkyl, C₄ to C₁₁ cycloalkylalkyl, aryl, or aryl(C₁-C₁₀ alkyl);

10 R^{5c} is selected from: H, halogen, C₁-C₄ alkyl, C₁-C₃ haloalkyl, CN, C₁-C₄ alkoxy, NO₂;

R⁸ is selected from:

H;

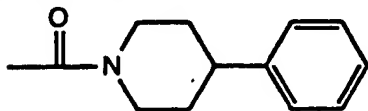
15 C₁-C₆ alkyl substituted with 0-4 R^{3a};
 C₂-C₆ alkenyl substituted with 0-4 R^{3a};
 C₂-C₆ alkynyl substituted with 0-4 R^{3a};
 C₃-C₈ cycloalkyl substituted with 0-4 R^{3a};
 aryl substituted with 0-4 R^{3a};
 20 aryl(C₁-C₆ alkyl)- substituted with 0-4 R^{3a};

a 5-10 membered heterocyclic ring system having 1-4 heteroatoms selected independently from O, S, and N, said heterocyclic ring being substituted with
 25 0-3 R^{3a};

C₁-C₆ alkyl substituted with a 5-10 membered heterocyclic ring system having 1-4 heteroatoms selected independently from O, S, and N, said
 30 heterocyclic ring being substituted with 0-4 R^{3a};

(R¹²) (R^{5a})NC(=O)-;

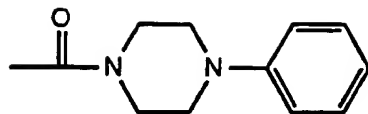
piperidyl-C(=O)-;



substituted with 0-4 R^{3a}; or

35

-178-

substituted with 0-4 R^{3a};

R^{3a} is selected from H, halogen, C₁-C₈ alkyl, C₂-C₆ alkenyl, C₃-C₁₁ cycloalkyl, C₄-C₁₁ cycloalkylalkyl, aryl, aryl(C₁-C₆ alkyl)-;

R⁹ is selected from:

H,
 -R¹⁵,
 10 -N(R^{6d})C(=O)-O-R^{15a},
 -N(R^{6d})C(=O)-R¹⁵,
 -N(R^{6d})C(=O)-NH-R¹⁵,
 -N(R^{6d})NH-C(=O)-O-R^{15a},
 -N(R^{6d})NH-C(=O)-R¹⁵,
 15 -N(R^{6d})NH-C(=O)-NH-R¹⁵,
 -N(R^{6d})S(=O)₂-O-R^{15b},
 -N(R^{6d})S(=O)₂-R¹⁵,
 -N(R^{6d})C(=S)NHR¹⁵,
 -N(R^{6d})P(=S)OR^{15a},
 20 -N(R^{6d})P(=O)OR^{15a},
 -N(R^{6d})P(=S)(R^{15a})₂,
 -N(R^{6d})P(=O)(R^{15a})₂,
 -N(R¹²)(R^{5a}),
 -CH=CH-R¹⁵, or
 25 -C≡C-R¹⁵;

with the proviso that when U is -C(=O)NH- or -C(=O)NHCH₂-, then R⁹ is not H;

30 R^{6d} is selected from: H, C₁-C₁₀ alkyl, C₂-C₆ alkenyl, C₃-C₁₁ cycloalkyl, C₄-C₁₅ cycloalkylalkyl, aryl, aryl(C₁-C₁₀ alkyl)-;

R¹⁵ is selected from:

35 H,

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C₁-C₈ alkyl substituted with 0-4 R^{3a},
C₂-C₈ alkenyl substituted with 0-4 R^{3a},
C₂-C₈ alkynyl substituted with 0-4 R^{3a},
C₃-C₈ cycloalkyl substituted with 0-4 R^{3a},
5 aryl substituted with 0-4 R^{3a},
aryl(C₁-C₆ alkyl)- substituted with 0-4 R^{3a},

10 a 5-10 membered heterocyclic ring system having 1-4
heteroatoms selected independently from O, S, and
N, said heterocyclic ring being substituted with
0-3 R^{3a},

15 C₁-C₆ alkyl substituted with a 5-10 membered
heterocyclic ring system having 1-4 heteroatoms
selected independently from O, S, and N, said
heterocyclic ring being substituted with 0-4 R^{3a};

R^{15a} is selected from:

20 C₁-C₈ alkyl substituted with 0-4 R^{3a},
C₂-C₈ alkenyl substituted with 0-4 R^{3a},
C₂-C₈ alkynyl substituted with 0-4 R^{3a},
C₃-C₈ cycloalkyl substituted with 0-4 R^{3a},
aryl substituted with 0-4 R^{3a},
aryl(C₁-C₆ alkyl)- substituted with 0-4 R^{3a},

25 a 5-10 membered heterocyclic ring system having 1-4
heteroatoms selected independently from O, S, and
N, said heterocyclic ring being substituted with
0-3 R^{3a},

30 C₁-C₆ alkyl substituted with a 5-10 membered
heterocyclic ring system having 1-4 heteroatoms
selected independently from O, S, and N, said
heterocyclic ring being substituted with 0-4 R^{3a};

35 R¹⁰ is selected from CO₂R¹⁶, CO₂R^{13b}, SO₃H, tetrazolyl,
or PO₃H;

-180-

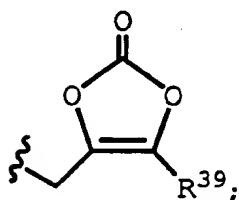
R^{16} is selected from: H, C_1 to C_{10} alkyl, C_3 to C_{11}
 cycloalkyl, aryl, aryl(C_1 to C_6 alkyl)-, C_3 to C_{10}
 alkylcarbonyloxyalkyl, C_3 to C_{10}
 5 alkoxy carbonyloxyalkyl, C_2 to C_{10} alkoxy carbonyl,
 C_5 to C_{10} cycloalkylcarbonyloxyalkyl, C_5 to C_{10}
 cycloalkoxy carbonyloxyalkyl, C_5 to C_{10}
 cycloalkoxy carbonyl, aryloxy carbonyl,
 aryloxy carbonyloxy(C_1 to C_6 alkyl)-,
 10 arylcarbonyloxy(C_1 to C_6 alkyl)-, C_5 to C_{12}
 alkoxyalkylcarbonyloxyalkyl, (5-(C_1 - C_5 alkyl)-1,3-
 dioxo-cyclopenten-2-one-yl)methyl, (5-aryl-1,3-
 dioxo-cyclopenten-2-one-yl)methyl, or
 (R^{12}) (R^{5a})N-(C_1 - C_{10} alkyl)-;

15

R^{13b} is selected independently from:

$-\text{CH}(R^{36})\text{OC}(=\text{O})R^{37};$
 $-\text{CH}(R^{36})\text{OC}(=\text{O})OR^{38};$

20



R^{36} is C_1 - C_4 linear alkyl or H;

25 R^{37} is selected from:

- (a) H;
- (b) C_1 - C_8 alkyl or C_3 - C_8 cycloalkyl, said alkyl or cycloalkyl being substituted with 1-2 groups independently selected from:
 - 30 (i) C_1 - C_4 alkyl;
 - (ii) C_3 - C_8 cycloalkyl;
 - (iii) C_1 - C_5 alkoxy;
 - (iv) aryl substituted with 0-2 groups independently selected from: halogen, phenyl,

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C₁-C₆ alkyl, C₁-C₆ alkoxy, NO₂, -S(C₁-C₅ alkyl), -S(=O)(C₁-C₅ alkyl), -SO₂(C₁-C₅ alkyl), -OH, -N(R¹²)(R^{5a}), -CO₂R^{5a}, -C(=O)N(R¹²)(R^{5a}), or -C_vF_w where v = 1 to 3 and w = 1 to (2v+1);

- 5 (c) aryl substituted with 0-2 groups independently selected from: halogen, phenyl, C₁-C₆ alkyl, C₁-C₆ alkoxy, NO₂, -S(C₁-C₅ alkyl), -S(=O)(C₁-C₅ alkyl), -SO₂(C₁-C₅ alkyl), -OH, -N(R¹²)(R^{5a}), -CO₂R^{5a}, -C(=O)N(R¹²)(R^{5a}), or
10 -C_vF_w where v = 1 to 3 and w = 1 to (2v+1);

R³⁸ is selected from:

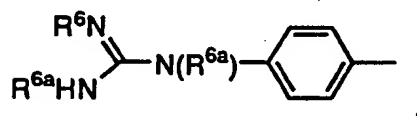
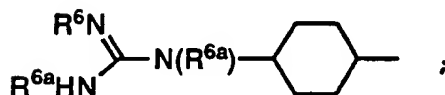
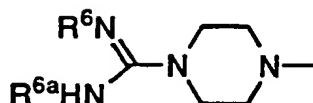
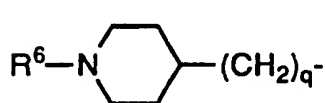
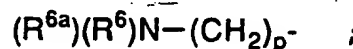
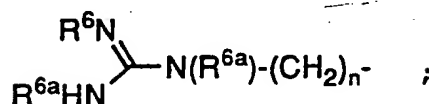
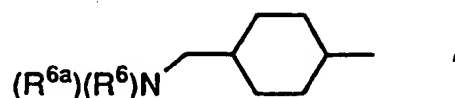
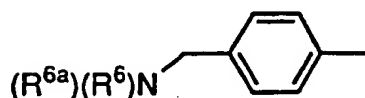
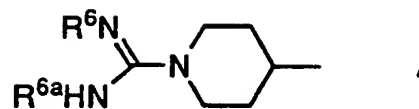
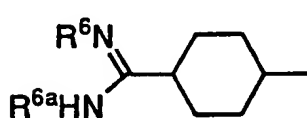
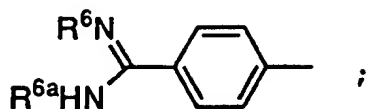
- (a) C₁-C₈ alkyl or C₃-C₈ cycloalkyl, said alkyl or cycloalkyl being substituted with 1-2 groups
15 independently selected from:
(i) C₁-C₄ alkyl;
(ii) C₃-C₈ cycloalkyl;
(iii) C₁-C₅ alkoxy;
(iv) aryl substituted with 0-2 groups
20 independently selected from: halogen, phenyl, C₁-C₆ alkyl, C₁-C₆ alkoxy, NO₂, -S(C₁-C₅ alkyl), -S(=O)(C₁-C₅ alkyl), -SO₂(C₁-C₅ alkyl), -OH, -N(R¹²)(R^{5a}), -CO₂R^{5a}, -C(=O)N(R¹²)(R^{5a}), or -C_vF_w where v = 1 to 3 and w = 1 to (2v+1);
25 (b) aryl substituted with 0-2 groups independently selected from: halogen, phenyl, C₁-C₆ alkyl, C₁-C₆ alkoxy, NO₂, -S(C₁-C₅ alkyl), -S(=O)(C₁-C₅ alkyl), -SO₂(C₁-C₅ alkyl), -OH, -N(R¹²)(R^{5a}), -CO₂R^{5a}, -C(=O)N(R¹²)(R^{5a}), or
30 -C_vF_w where v = 1 to 3 and w = 1 to (2v+1);

R³⁹ is C₁-C₄ alkyl, benzyl, or phenyl.

- 35 2. A compound of Claim 1 of Formula I, or a pharmaceutically acceptable salt form thereof, wherein:

-182-

R¹ is selected from:



10

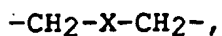
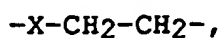
R^{6e}, R⁷, and R^{7a} are H;

R^{6a} is H or C₁-C₄ alkyl;

15 alternatively, R^{6e} and R⁷ can be taken together with the nitrogen and carbon atom to which they are attached to form a 5-7 membered nitrogen heterocycle, said heterocycle optionally including one additional N, O or S atom;

20

U is selected from:



25

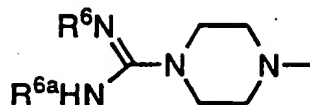


-183-

-CH₂-CH=CH-,
 -CH=CH-CH₂-,
 -CH₂-C≡C-,
 -C≡C-CH₂-,
 5 -CH=CH-,
 -C≡C-,
 -CH₂-CH₂-,
 -X-CH₂-,
 -CH₂-X-,
 10 -X-,
 -CH₂-;

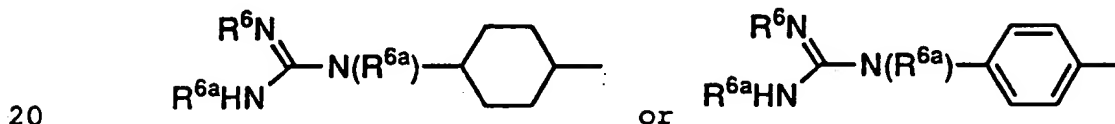
X is selected from: O, S, S(=O), SO₂, N(R^{6c});

15 with the proviso that when R¹ is



then X is not S or S(=O);

with the proviso that when R¹ is



then U is not -CH₂-CH₂-CH₂-, -X-CH₂-CH₂-,
 -CH₂-X-CH₂-, -CH₂-CH₂-X-, -CH₂-CH=CH-,
 -CH=CH-CH₂-, -CH₂-C≡C-, or -C≡C-CH₂-;

25 R^{6c} is selected from H or C₁-C₄ alkyl;

Q is a heterocycle selected from oxazole, isoxazole,
 oxazoline, isoxazoline, thiazole, isothiazole,
 thiazoline, isothiazoline, triazole, imidazole,
 30 imidazoline, 1,2,4-oxadiazole, 1,2,4-thiadiazole,
 1,3,4-oxadiazole, 1,3,4-thiadiazole, thiophene,
 furan, or pyrrole, said heterocycle being
 substituted with 0-2 R⁵, wherein the bonds between

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Q and Y and between Q and U are at the 1 and 3 positions of Q;

5 R^5 is independently selected from: H, halo, cyano, CO_2R^{5a} , OR^{5a} , $OCH_2CO_2R^{5a}$, NO_2 , $(C_1-C_{10}$ alkyl)carbonyl, $-N(R^{12})R^{5a}$, C_1-C_{10} alkyl, C_2-C_6 alkenyl, C_4 to C_{11} cycloalkylmethyl, C_3 to C_{10} cycloalkyl, aryl, aryl(C_1-C_6 alkyl)-,

10 aryl substituted with 0-3 R^{5c} ;

R^{5a} is selected from: H, C_1 to C_{10} alkyl, C_2 to C_6 alkenyl, C_4 to C_{11} cycloalkylmethyl, aryl(C_1-C_6 alkyl)-;

15

R^{5c} is selected from: H, halogen, C_1-C_4 alkyl, C_1-C_3 haloalkyl, CN, C_1-C_4 alkoxy, NO_2 ;

R^8 is selected from:

20

H;

 C_1-C_6 alkyl substituted with 0-4 R^{3a} ; C_2-C_6 alkenyl substituted with 0-4 R^{3a} ; C_2-C_6 alkynyl substituted with 0-4 R^{3a} ; C_3-C_8 cycloalkyl substituted with 0-4 R^{3a} ;

25

aryl substituted with 0-2 R^{3a} ;aryl(C_1-C_6 alkyl)- substituted with 0-2 R^{3a} ;

30

a heterocyclic ring system selected from pyridinyl, furanyl, thiazolyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, benzofuranyl, indolyl, indolenyl, quinolinyl, isoquinolinyl, benzimidazolyl, piperidinyl, tetrahydrofuranyl, pyranyl, pyridinyl, 3H-indolyl, indolyl, carbazole, pyrrolidinyl, piperidinyl, indolinyl, or morpholinyl, said

35

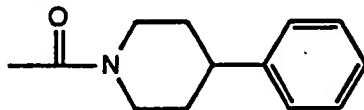
heterocyclic ring being substituted with 0-2 R^{3a} ;

-185-

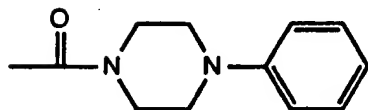
C₁-C₆ alkyl substituted with a heterocyclic ring system selected from pyridinyl, furanyl, thiazolyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, benzofuranyl, indolyl, indolenyl, quinolinyl, isoquinolinyl, benzimidazolyl, piperidinyl, tetrahydrofuranyl, pyranyl, pyridinyl, 3H-indolyl, indolyl, carbazole, pyrrolidinyl, piperidinyl, indolinyl, or morpholinyl, , said heterocyclic ring being substituted with 0-2 R^{3a};

(R¹²) (R^{5a})NC(=O)-;

piperidyl-C(=O)-;



substituted with 0-2 R^{3a}; or



substituted with 0-2 R^{3a};

R¹² and R¹³ are independently selected from: H, C₁-C₁₀ alkyl, aryl, C₂-C₆ alkenyl, C₄-C₁₁ cycloalkylalkyl, aryl(C₁-C₆ alkyl)-;

R^{3a} is selected from H, C₁-C₈ alkyl, C₂-C₆ alkenyl, C₃-C₁₁ cycloalkyl, C₄-C₁₁ cycloalkylalkyl, aryl, aryl(C₁-C₆ alkyl)-;

R⁹ is selected from:

H,
 -R¹⁵,
 -N(R^{6d})C(=O)-O-R^{15a},
 -N(R^{6d})C(=O)-R¹⁵,
 -N(R^{6d})C(=O)-NH-R¹⁵,
 -N(R^{6d})NH-C(=O)-O-R^{15a},
 -N(R^{6d})NH-C(=O)-R¹⁵,
 -N(R^{6d})NH-C(=O)-NH-R¹⁵,

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-N(R^{6d})S(=O)₂-R¹⁵,
-N(R¹²)(R^{5a}),
-CH=CH-R¹⁵, or
-C≡C-R¹⁵;

5

R^{6d} is selected from: H or C₁-C₄ alkyl;

R¹⁵ is selected from:

- H,
10 C₁-C₈ alkyl substituted with 0-4 R^{3a},
C₂-C₈ alkenyl substituted with 0-4 R^{3a},
C₃-C₈ cycloalkyl substituted with 0-2 R^{3a},
aryl substituted with 0-2 R^{3a},
aryl(C₁-C₆ alkyl)- substituted with 0-2 R^{3a},
15
a heterocyclic ring system selected from pyridinyl,
furanyl, thiazolyl, thienyl, pyrrolyl, pyrazolyl,
imidazolyl, benzofuranyl, indolyl, indolenyl,
quinolinyl, isoquinolinyl, benzimidazolyl,
20 piperidinyl, tetrahydrofuranyl, pyranal, pyridinyl,
3H-indolyl, indolyl, carbazole, pyrrolidinyl,
piperidinyl, indolinyl, or morpholinyl, said
heterocyclic ring being substituted with 0-2 R^{3a},
25 C₁-C₆ alkyl substituted with a heterocyclic ring
system selected from pyridinyl, furanyl, thiazolyl,
thienyl, pyrrolyl, pyrazolyl, imidazolyl,
benzofuranyl, indolyl, indolenyl, quinolinyl,
isoquinolinyl, benzimidazolyl, piperidinyl,
30 tetrahydrofuranyl, pyranal, pyridinyl, 3H-indolyl,
indolyl, carbazole, pyrrolidinyl, piperidinyl,
indolinyl, or morpholinyl, said heterocyclic ring
being substituted with 0-2 R^{3a};

35 R^{15a} is selected from:

C₁-C₈ alkyl substituted with 0-4 R^{3a},
C₂-C₈ alkenyl substituted with 0-4 R^{3a},

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C₃-C₈ cycloalkyl substituted with 0-2 R^{3a},
aryl substituted with 0-2 R^{3a},
aryl(C₁-C₆ alkyl)- substituted with 0-2 R^{3a},

5 a heterocyclic ring system selected from pyridinyl,
furanyl, thiazolyl, thienyl, pyrrolyl, pyrazolyl,
imidazolyl, benzofuranyl, indolyl, indolenyl,
quinolinyl, isoquinolinyl, benzimidazolyl,
piperidinyl, tetrahydrofuranyl, pyranyl, pyridinyl,
10 3H-indolyl, indolyl, carbazole, pyrrolidinyl,
piperidinyl, indolinyl, or morpholinyl, said
heterocyclic ring being substituted with 0-2 R^{3a},

C₁-C₆ alkyl substituted with a heterocyclic ring
15 system selected from pyridinyl, furanyl, thiazolyl,
thienyl, pyrrolyl, pyrazolyl, imidazolyl,
benzofuranyl, indolyl, indolenyl, quinolinyl,
isoquinolinyl, benzimidazolyl, piperidinyl,
tetrahydrofuranyl, pyranyl, pyridinyl, 3H-indolyl,
20 indolyl, carbazole, pyrrolidinyl, piperidinyl,
indolinyl, or morpholinyl, said heterocyclic ring
being substituted with 0-2 R^{3a};

R¹⁰ is selected from CO₂R¹⁶;

25

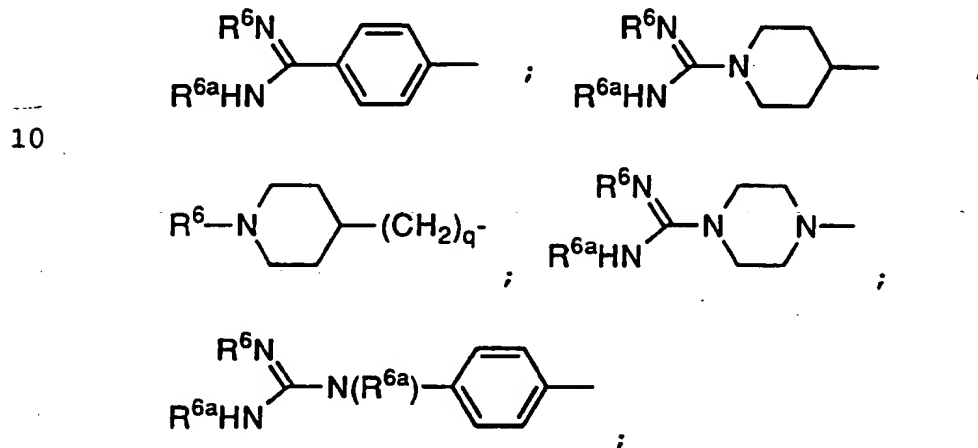
R¹⁶ is selected from: H, C₁ to C₁₀ alkyl, C₃ to C₁₁
cycloalkyl, aryl, aryl(C₁ to C₆ alkyl)-, C₃ to C₁₀
alkylcarbonyloxyalkyl, C₃ to C₁₀
alkoxycarbonyloxyalkyl, C₂ to C₁₀ alkoxycarbonyl,
30 C₅ to C₁₀ cycloalkylcarbonyloxyalkyl, C₅ to C₁₀
cycloalkoxycarbonyloxyalkyl, C₅ to C₁₀
cycloalkoxycarbonyl, aryloxy carbonyl,
aryloxy carbonyloxy(C₁ to C₆ alkyl)-,
arylcarbonyloxy(C₁ to C₆ alkyl)-, C₅ to C₁₂
35 alkoxyalkylcarbonyloxyalkyl, (5-(C₁-C₅ alkyl)-1,3-
dioxo-cyclopenten-2-one-yl)methyl, (5-aryl-1,3-

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dioxa-cyclopenten-2-one-yl)methyl, or
 (R¹²) (R^{5a})N-(C₁-C₁₀ alkyl)-.

3. A compound of Claim 1, or a pharmaceutically
 5 acceptable salt form thereof, wherein:

R¹ is selected from:



15 R^{6a}, R^{6e}, R⁷, and R^{7a} are H;

R⁶ is H or C₁-C₄ alkyl;

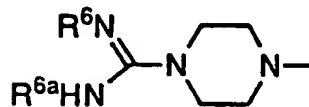
U is selected from:

20 -CH=CH-,
 -C≡C-,
 -CH₂-CH₂-,
 -X-CH₂-,
 -CH₂-X-;

25

X is selected from: O, S, S(=O), SO₂, N(R^{6c});

with the proviso that when R¹ is



30

then X is not S or S(=O);

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R^{6c} is H or C₁-C₄ alkyl;

V is -Q-Y-;

5

Y is -C(=O)-;

Q is a heterocycle selected from oxazole, isoxazole,
oxazoline, isoxazoline, thiazole, isothiazole,
10 thiazoline, isothiazoline, triazole, imidazole,
imidazoline, 1,2,4-oxadiazole, 1,2,4- thiadiazole,
1,3,4-oxadiazole, 1,3,4-thiadiazole, thiophene,
furan, or pyrrole, said heterocycle being
substituted with 0-2 R⁵, wherein the bonds between
15 Q and Y and between Q and U are at the 1 and 3
positions of Q;

R⁵ is independently selected from: H, halo, cyano,
C₁-C₁₀ alkyl, OR^{5a}, OCH₂CO₂R^{5a}, NO₂, -N(R¹²)R^{5a}, C₄
20 to C₁₁ cycloalkylmethyl, aryl, aryl(C₁-C₆ alkyl)-,
aryl substituted with 0-3 R^{5c};

R^{5a} is selected from: H, C₁ to C₁₀ alkyl, C₂ to C₆
25 alkenyl, C₄ to C₁₁ cycloalkylmethyl,
aryl(C₁-C₆ alkyl)-;

R^{5c} is selected from: H, halo, cyano, C₁-C₄ alkyl, C₂-C₄
alkenyl, C₁-C₄ alkoxy, NO₂;

30

R⁸ is H or C₁-C₆ alkyl;

R⁹ is selected from:

-R¹⁵,
35 -N(R^{6d})C(=O)-O-R^{15a},
-N(R^{6d})C(=O)-R¹⁵,
-N(R^{6d})S(=O)₂-R¹⁵,

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 $-N(R^{12})(R^{13})$; R^{6d} is H;

- 5 R^{12} and R^{13} are independently selected from: H, C_1 - C_{10} alkyl, C_2 - C_6 alkenyl, C_4 - C_{11} cycloalkylalkyl, aryl(C_1 - C_6 alkyl)-;

 R^{15} is selected from:

- 10 H,
 C_1 - C_8 alkyl,
 C_3 - C_8 cycloalkyl,
aryl substituted with 0-2 R^{3a} ,
aryl(C_1 - C_6 alkyl)- substituted with 0-2 R^{3a} ,
- 15 a heterocyclic ring system selected from pyridinyl, furanyl, thiazolyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, benzofuranyl, indolyl, indolenyl, quinolinyl, isoquinolinyl, benzimidazolyl,
- 20 piperidinyl, tetrahydrofuranyl, pyranyl, pyridinyl, 3H-indolyl, indolyl, carbazole, pyrrolidinyl, piperidinyl, indolinyl, or morpholinyl, said heterocyclic ring being substituted with 0-2 R^{3a} ,
- 25 C_1 - C_6 alkyl substituted with a heterocyclic ring system selected from pyridinyl, furanyl, thiazolyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, benzofuranyl, indolyl, indolenyl, quinolinyl, isoquinolinyl, benzimidazolyl, piperidinyl,
- 30 tetrahydrofuranyl, pyranyl, pyridinyl, 3H-indolyl, indolyl, carbazole, pyrrolidinyl, piperidinyl, indolinyl, or morpholinyl, said heterocyclic ring being substituted with 0-2 R^{3a} ;
- 35 R^{3a} is selected from: H, C_1 - C_8 alkyl, C_2 - C_6 alkenyl, C_3 - C_{11} cycloalkyl, C_4 - C_{11} cycloalkylalkyl, aryl, aryl(C_1 - C_6 alkyl)-;

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R^{15a} is selected from:

- 5 C₁-C₈ alkyl substituted with 0-4 R^{3a},
C₃-C₈ cycloalkyl substituted with 0-2 R^{3a},
aryl substituted with 0-2 R^{3a},
aryl(C₁-C₆ alkyl)- substituted with 0-2 R^{3a},

10 a heterocyclic ring system selected from pyridinyl,
furanyl, thiazolyl, thienyl, pyrrolyl, pyrazolyl,
imidazolyl, benzofuranyl, indolyl, indolenyl,
quinolinyl, isoquinolinyl, benzimidazolyl,
piperidinyl, tetrahydrofuranyl, pyranal, pyridinyl,
3H-indolyl, indolyl, carbazole, pyrrolidinyl,
15 piperidinyl, indolinyl, or morpholinyl, said
heterocyclic ring being substituted with 0-2 R^{3a},

20 C₁-C₆ alkyl substituted with a heterocyclic ring
system selected from pyridinyl, furanyl, thiazolyl,
thienyl, pyrrolyl, pyrazolyl, imidazolyl,
benzofuranyl, indolyl, indolenyl, quinolinyl,
isoquinolinyl, benzimidazolyl, piperidinyl,
tetrahydrofuranyl, pyranal, pyridinyl, 3H-indolyl,
indolyl, carbazole, pyrrolidinyl, piperidinyl,
indolinyl, or morpholinyl, said heterocyclic ring
25 being substituted with 0-2 R^{3a};

R¹⁰ is selected from CO₂R¹⁶;

R¹⁶ is selected from:

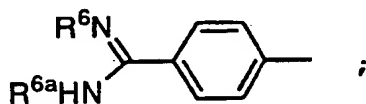
- 30 H;
C₁ to C₁₀ alkyl;
methylcarbonyloxymethyl-;
ethylcarbonyloxymethyl-;
t-butylcarbonyloxymethyl-;
35 cyclohexylcarbonyloxymethyl-;
1-(methylcarbonyloxy)ethyl-;
1-(ethylcarbonyloxy)ethyl-;

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- 1-(*t*-butylcarbonyloxy)ethyl-;
 1-(cyclohexylcarbonyloxy)ethyl-;
i-propyloxy carbonyloxymethyl-;
 cyclohexylcarbonyloxymethyl-;
 5 *t*-butyloxy carbonyloxymethyl-;
 1-(*i*-propyloxy carbonyloxy)ethyl-;
 1-(cyclohexyloxy carbonyloxy)ethyl-;
 1-(*t*-butyloxy carbonyloxy)ethyl-;
 dimethylaminoethyl-;
 10 diethylaminoethyl-;
 (1,3-dioxa-5-methyl-cyclopenten-2-one-4-yl)methyl-;
 (5-(*t*-butyl)-1,3-dioxa-cyclopenten-2-one-4-yl)methyl-;
 (1,3-dioxa-5-phenyl-cyclopenten-2-one-4-yl)methyl-;
 15 1-(2-(2-methoxypropyl) carbonyloxy)ethyl-.

4. A compound of Claim 1, or a pharmaceutically acceptable salt form thereof, wherein:

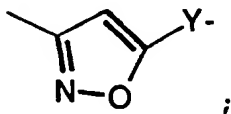
20 R^1 is



R^6 , R^{6a} , R^{6e} , R^7 , and R^{7a} are H;

25 U is -O-CH₂- or -CH₂-O-;

V is



30 Y is -C(=O)-;

R^8 is H or C₁-C₄ alkyl;

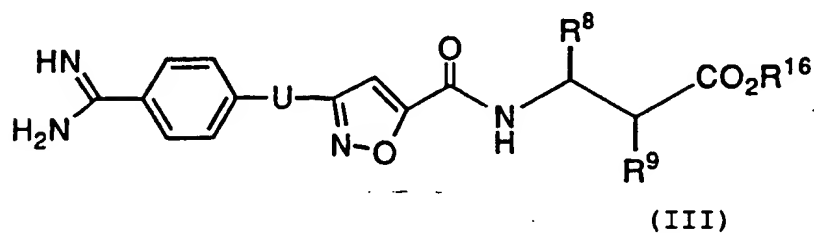
-193-

R^9 is selected from: $-NHSO_2$ -phenyl, $-NH$ -Tosyl,
 $-NHSO_2(C_1-C_6 \text{ alkyl})-$, $-NH$ -Cbz, $-NHC(=O)(C_1-C_6$
 alkoxy), $-NHC(=O)(C_1-C_6 \text{ alkyl})$, $-NHC(=O)$ -aryl,
 $-NHC(=O)O-(C_1-C_6 \text{ alkyl})$ aryl, $-NH(C=O)-(C_1-C_6$
 alkyl)aryl, $-NHC(=O)$ -3-pyridyl;

R^{10} is CO_2R^{16} ;

R^{16} is H or C_1 to C_6 alkyl.

5. A compound of Claim 1 of Formula III:



or a pharmaceutically acceptable salt form thereof,
 selected from:

the compound wherein U is OCH_2 , R^8 is CH_3 , R^9 is H, and
 R^{16} is H;

the compound wherein U is OCH_2 , R^8 is H, R^9 is $-NH$ -Cbz,
 and R^{16} is H;

the compound wherein U is OCH_2 , R^8 is H, R^9 is $-NH$ -Cbz,
 and R^{16} is CH_3 ;

the compound wherein U is OCH_2 , R^8 is H, R^9 is $-NH$ -Cbz,
 and R^{16} is CH_2CH_3 ;

the compound wherein U is CH_2O , R^8 is CH_3 , R^9 is H, and
 R^{16} is H;

the compound wherein U is CH_2O , R^8 is CF_3 , R^9 is H, and
 R^{16} is H;

the compound wherein U is OCH_2 , R^8 is H, R^9 is H, and R^{16}
 is H;

the compound wherein U is OCH_2 , R^8 is H, R^9 is $-NH$ -Tosyl,
 and R^{16} is H;

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- the compound wherein U is OCH₂, R⁸ is H, R⁹ is -NH-Tosyl, and R¹⁶ is CH₃;
- the compound wherein U is OCH₂, R⁸ is H, R⁹ is -NH-SO₂(CH₂)₃CH₃, and R¹⁶ is H;
- 5 the compound wherein U is OCH₂, R⁸ is H, R⁹ is -NH-SO₂(CH₂)₃CH₃, and R¹⁶ is CH₃;
- the compound wherein U is OCH₂, R⁸ is H, R⁹ is -NH-C(=O)O-C(CH₃)₃, and R¹⁶ is H;
- the compound wherein U is OCH₂, R⁸ is H, R⁹ is -NH-C(=O)O-C(CH₃)₃, and R¹⁶ is CH₃;
- 10 the compound wherein U is OCH₂, R⁸ is H, R⁹ is -NH-C(=O)-(CH₂)₃CH₃, and R¹⁶ is H;
- the compound wherein U is OCH₂, R⁸ is H, R⁹ is -NH-C(=O)-(CH₂)₃CH₃, and R¹⁶ is CH₃;
- 15 the compound wherein U is OCH₂, R⁸ is H, R⁹ is -NH-C(=O)-O(CH₂)₃CH₃, and R¹⁶ is H;
- the compound wherein U is OCH₂, R⁸ is H, R⁹ is -NH-C(=O)-O(CH₂)₃CH₃, and R¹⁶ is CH₃;
- the compound wherein U is OCH₂, R⁸ is H, R⁹ is -NH-C(=O)-(CH₂)₂CH₃, and R¹⁶ is H;
- 20 the compound wherein U is OCH₂, R⁸ is H, R⁹ is -NH-C(=O)-(CH₂)₂CH₃, and R¹⁶ is CH₃;
- the compound wherein U is OCH₂, R⁸ is H, R⁹ is -NH-C(=O)-3-pyridyl, and R¹⁶ is H;
- 25 the compound wherein U is OCH₂, R⁸ is H, R⁹ is -NH-C(=O)-3-pyridyl, and R¹⁶ is CH₃;
- the compound wherein U is OCH₂, R⁸ is H, R⁹ is -NH-C(=O)-(CH₂)₂-phenyl, and R¹⁶ is H;
- the compound wherein U is OCH₂, R⁸ is H, R⁹ is -NH-C(=O)-(CH₂)₂-phenyl, and R¹⁶ is CH₃;
- 30 the compound wherein U is OCH₂, R⁸ is H, R⁹ is -NH₂, and R¹⁶ is H;
- the compound wherein U is OCH₂, R⁸ is H, R⁹ is -NH₂, and R¹⁶ is CH₃.

35

6. A method for the treatment of thromboembolic disorders which comprises administering to a host in

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need of such treatment a therapeutically effective amount of a compound of Claim 1.

7. A method for the treatment of thromboembolic disorders which comprises administering to a host in need of such treatment a therapeutically effective amount of a compound of Claim 2.

8. A method for the treatment of thromboembolic disorders which comprises administering to a host in need of such treatment a therapeutically effective amount of a compound of Claim 3.

9. A method for the treatment of thromboembolic disorders which comprises administering to a host in need of such treatment a therapeutically effective amount of a compound of Claim 4.

10. A method for the treatment of thromboembolic disorders which comprises administering to a host in need of such treatment a therapeutically effective amount of a compound of Claim 5.

11. A pharmaceutical composition comprising therapeutically effective amount of a compound of Claim 1 and a pharmaceutically effective carrier.

12. A pharmaceutical composition comprising therapeutically effective amount of a compound of Claim 2 and a pharmaceutically effective carrier.

13. A pharmaceutical composition comprising therapeutically effective amount of a compound of Claim 3 and a pharmaceutically effective carrier.

35

14. A pharmaceutical composition comprising therapeutically effective amount of a compound of

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Claim 4 and a pharmaceutically effective carrier.

15. A pharmaceutical composition comprising therapeutically effective amount of a compound of
5 Claim 5 and a pharmaceutically effective carrier.

16. A method of inhibiting the binding of fibrinogen to blood platelets in a mammal which comprises administering to a mammal in need of such
10 inhibition a therapeutically effective amount of a compound of Claim 1.

17. A method of inhibiting the aggregation of blood platelets in a mammal which comprises
15 administering to a mammal in need of such inhibition a therapeutically effective amount of a compound of Claim 1.

18. A method of treating thrombus or embolus
20 formation in a mammal which comprises administering to a mammal in need of such treatment a therapeutically effective amount of a compound of Claim 1.

19. A method of preventing thrombus or embolus
25 formation in a mammal which comprises administering to a mammal in need of such prevention a therapeutically effective amount of a compound of Claim 1.

20. A method for the treatment of thromboembolic
30 disorders in a mammal which comprises administering to a mammal in need of such treatment a therapeutically effective amount of a compound of Claim 1 in combination with one or more additional therapeutic agents selected from: a thrombolytic agent, an anti-coagulant agent, or
35 an anti-platelet agent.

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21. A method according to Claim 20 wherein the thrombolytic agent is plasminogen activator or streptokinase, the anti-coagulant agent is heparin or warfarin, and the anti-platelet agent is aspirin.

5

22. A pharmaceutical kit for the treatment of thromboembolic disorders comprising one or more containers containing pharmaceutical dosage units comprising a compound of Formula I of Claim 1.

INTERNATIONAL SEARCH REPORT

I. national Application No
PCT/US 94/14244

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D261/18 A61K31/42 C07D413/12 C07D307/68 C07D333/38
C07D277/56 C07D263/34 C07D207/34 C07D207/38

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP,A,0 513 810 (MONSANTO COMPANY) 19 November 1992 see claims ---	1-22
A	EP,A,0 540 334 (MERCK AND CO. INC.) 5 May 1993 see claims ---	1-22
A	EP,A,0 478 328 (MERCK AND CO. INC.) 1 April 1992 see claims ---	1-22
A	WO,A,92 15607 (G.D. SEARLE AND CO) 17 September 1992 see claims --- -/--	1-22

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
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- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

& document member of the same patent family

Date of the actual completion of the international search

23 February 1995

Date of mailing of the international search report

6. 03. 95

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Authorized officer

Henry, J

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 94/14244

(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,A	CHEMICAL ABSTRACTS, vol. 120, no. 11, 14 March 1994, Columbus, Ohio, US; abstract no. 134060z, page 994 ;column 1 ; see abstract	1-22
A	& JP,A,5 230 009 (TAISHO PHARMA CO LTD) 7 September 1993 -----	1-22

Box I: Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 6-10 and 16-21 are directed to a method of treatment of the human body the search has been carried out and based on the alleged effects of the compounds.
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
The formulation of the claims is so complicated because of the distinct combinations of the meanings of the variable parts that it does not comply with Art. 6 PCT prescribing that the claims shall be clear and concise. For these reasons the search has been limited to the examples.
3. ☐ Claims searched incompletely: 1-3,6-8,11-13,16-22
Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II: Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 94/14244

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